TÜRK YOĞUN BAKIM DERGİSİ

TURKISH JOURNAL OF INTENSIVE CARE

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

E-ISSN: 2602-2974

CİLT / VOLUME 22
SAYI / ISSUE 4
ARALIK / DECEMBER 2024

REWIEW / DERLEME

ORIGINAL RESEARCHES / ÖZGÜN ARAŞTIRMALAR

galenos yayınevi

Vedanın Geçici Hali

Ülkemizin yoğun bakım toplumuna ve dünyanın tüm yoğun bakım toplumlarına, yoğun bakımın hedefini ve felsefesini çizerek, yazarak, anlatarak, yaşayarak öğreten filozof Luciano Gattinioni aramızdan ayrıldı.

Kutay abi, Jozef ve ben onunla 1989 yılının ilk ayında tanıştık. O gün çok özgün bir karakter ile karşı karşıya olduğumuzu anlamıştık. Kendi adımıza, gerçekte Türk yoğun bakım toplumu adına, yoğun bakım biliminin en önemli bilim adamını-hocamızı bulmuştuk ve gitmemiz gereken yolu da saptamıştık. Yol alırken gördük ki, Gattinioni bilim adamından öte, özünde bir yoğun bakım filozofu. Her olguya, yayına, konuşmalara, anlatılarına kattığı düşüncelerin felsefi bir temeli olmuştur. Bizlere günü değil hep geleceği göstermiştir.

Hayran kaldığımız bu yoğun bakım filozofunu, Türk yoğun bakım toplumu da görsün, dinlesin, tanısın istedik. Her davetimize koşulsuz katılarak, uluslararası hocalığın en etkin, en etik modelini bizlere sundu. Türk yoğun bakım toplumu, filozof Gattinioni'yi unutmaz unutamaz.

Bilim adamları yayınlarda, kitaplarda, görsellerde kısaca bir yerde kalıcı olurlar. Yoğun bakım filozofu Gattinioni ise, yoğun bakımın atmosferine diffüz ettiği için her zaman yanımızda yer alacaktır.

Vedamız geçici, birlikteliğimiz kalıcı olacaktır.

Lütfi Telci

Jozef Kesecioğlu

Temporary Farewell

Philosopher Luciano Gattinioni, who taught the goal and philosophy of intensive care to the intensive care society of our country and to all the intensive care societies of the world by drawing, writing, explaining and experiencing, has passed away.

Professor Akpir and we met him in the first month of 1989. That day, we realised that we were faced with a very unique person. On our own behalf, and in fact on behalf of the Turkish intensive care community, we had found the most important scientist- tutor of intensive care medicine and determined the path we needed to follow thereafter. As we progressed, we saw that Gattinioni was more than a scientist, but essentially an intensive care philosopher. The ideas he brought to every case, publication, speech, and narrative had a philosophical basis. He showed us the future, not the present.

We wanted the Turkish intensive care community to see, listen to and get to know this intensive care philosopher whom we admire. By attending every invitation unconditionally, he presented us with the most effective and ethical model of international teaching. The Turkish intensive care community will never forget the philosopher Gattinioni.

Scientists become permanent in publications, books, and images. Gattinioni, the philosopher of intensive care, will always be with us as he diffuses into the atmosphere of intensive care.

Our farewell will be temporary, our togetherness will be permanent.

Lütfi Telci

Jozef Kesecioğlu

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 22
SAYI / ISSUE 4
ARALIK / DECEMBER 2024

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

Yazışma Adresi / Correspondence Address
Türk Yoğun Bakım Derneği
İnönü Cad., Işık Apt., No: 53 Kat: 4 Gümüşsuyu, 34437 Taksim, İstanbul, Türkiye
Tel.: +90 212 292 92 70
Faks: +90 212 292 92 71
E-posta: dergi@yogunbakim.org.tr - info@yogunbakim.org.tr
URL: http://www.yogunbakimderg.com

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Telefon/Phone: +90 530 177 30 97 / +90 539 307 32 03
E-posta/E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Yayıncı Sertifika No/Publisher Certificate Number: 14521

Online Yayınlanma Tarihi/Online Publication Date: Aralık 2024/December 2024
E-ISSN: 2602-2974

Üç ayda bir yayımlanan süreli yayındır.
International scientific journal published quarterly.

TURKISH JOURNAL OF INTENSIVE CARE

CİLT / VOLUME 22
SAYI / ISSUE 4
ARALIK / DECEMBER 2024

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK YOĞUN BAKIM DERGİSİ

Derginin "Amaç ve Kapsam", "Yazarlara Bilgi" ve "Yayın Etiği" konularında bilgi almak için lütfen web sayfasına **(https://www.turkishjic.org/)** başvurun.

Derginin editöryal ve yayın süreçleri ile etik kuralları ICMJE, WAME, CSE, COPE, EASE ve NISO gibi uluslararası kuruluşların kurallarına uygun olarak şekillenmektedir. Dergimiz, "şeffaf olma ilkeleri ve akademik yayıncılıkta en iyi uygulamalar ilkeleri" ile uyum içindedir.

Türk Yoğun Bakım Dergisi, **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, CINAHL, Tübitak/Ulakbim, Türk Tıp Dizini, Türkiye Atıf Dizini, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline, Embase** ve **Türk Medline**'da indekslenmektedir.

Dergi elektronik olarak yayınlanmaktadır.

İmtiyaz Sahibi: Türk Yoğun Bakım Derneği Adına Tuğhan UTKU

Baş Editör: Perihan ERGİN ÖZCAN

Please refer to the journal's webpage **(https://www.turkishjic.org/)** for "Aims and Scope", "Instructions to Authors" and "Ethical Policy".

The editorial and publication process of the Turkish Journal of Intensive Care are shaped in accordance with the guidelines of ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Turkish Journal of Intensive Care is indexed in **Emerging Sources Citation Index (ESCI), ProQuest Health & Medical Complete, EBSCO Database, Gale, CINAHL, Tübitak/Ulakbim Turkish Medical Database, Turkiye Citation Index, Hinari, GOALI, ARDI, OARE, AGORA, J-Gate, IdealOnline, Embase** and **Turk Medline**.

The journal is published electronically.

Owner: Tuğhan UTKU on Behalf of Turkish Society of Intensive Care

Responsible Manager: Perihan ERGİN ÖZCAN

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 22
SAYI / ISSUE 4
ARALIK / DECEMBER 2024

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

İÇİNDEKİLER/CONTENTS

TURKISH JOURNAL
OF INTENSIVE CARE

CİLT / VOLUME 22
SAYI / ISSUE 4
ARALIK / DECEMBER 2024

TYBD
Türk Yoğun Bakım Derneği
Turkish Society of Intensive Care

TÜRK
YOĞUN
BAKIM
DERGİSİ

İÇİNDEKİLER/CONTENTS

DİZİN/INDEX

Turk J Intensive Care 2024;22:225-38
DOI: 10.4274/tybd.galenos.2024.50490

REVIEW / *DERLEME*

Lizbeth Hu,
Moodakare Ashwini Bhat,
Kellie Marie Jaremko

Role of Regional Anesthesia in Intensive Care: An Updated Narrative Review

Yoğun Bakımda Bölgesel Anestezinin Rolü: Güncellenmiş Bir Derleme

Received/Geliş Tarihi : 31.10.2024
Accepted/Kabul Tarihi : 18.11.2024

Lizbeth Hu,
Department of Anesthesiology and Pain Medicine, Columbia University Irving Medical Center, New York, USA

Moodakare Ashwini Bhat, Kellie Marie Jaremko
Department of Anesthesiology and Critical Care Medicine Johns Hopkins University Faculty of Medicine Baltimore, USA

Lec, Kellie Marie Jaremko MD (✉),
Department of Anesthesiology and Critical Care Medicine Johns Hopkins University Faculty of Medicine Baltimore, USA

E-mail : kjaremk1@jh.edu
ORCID ID : orcid.org/0000-0001-9342-1979

ABSTRACT *Objective:* This review aims to provide a synopsis of regional analgesic modalities in the intensive care unit (ICU) context and to evaluate existing literature regarding the benefits and limitations of performing these procedures in critically ill patients. Specifically, we review regional techniques in the setting of traumatic rib fractures and extremity fractures, thoracic surgery, major abdominal surgery, and cardiac surgery. We additionally discuss the limitations of clinical practice in performing regional anesthesia in the ICU setting. Overall, the current literature demonstrates promising benefits of regional analgesia in critically ill patients. However, more extensive high-powered studies are needed to determine optimal analgesic strategies in this tenuous population.
Keywords: Regional anesthesia, intensive care unit, acute pain, pain management, post-traumatic pain

ÖZ *Amaç:* Bu incelemenin amacı, yoğun bakım ünitesi (YBÜ) bağlamında bölgesel analjezik modalitelerinin bir özetini sunmak ve bu prosedürlerin kritik hastalarda gerçekleştirilmesinin faydaları ve sınırlamaları ile ilgili mevcut literatürü değerlendirmektir. Çalışmamızda özellikle travmatik kaburga ve ekstremite kırıkları, torasik cerrahi, majör abdominal cerrahi ve kalp cerrahisi için bölgesel teknikleri gözden geçirildi. Ayrıca, YBÜ ortamında bölgesel anestezi gerçekleştirirken klinik uygulamanın sınırlamaları da tartışıldı. Genel olarak, mevcut literatür, kritik hastalarda bölgesel analjezinin ümit verici faydalarını göstermektedir. Ancak, bu hassas popülasyon için optimum analjezik stratejileri belirlemek için daha kapsamlı, yüksek güçlü çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Bölgesel anestezi, yoğun bakım ünitesi, akut ağrı, ağrı yönetimi, travma sonrası ağrı

Introduction

Pain is pervasive and burdensome for critically ill patients. Approximately 50-70% of patients in intensive care units (ICUs) suffer from pain (1-3) -a figure likely underestimated considering the prevalence of mechanical ventilation, sedation, and delirium in these populations (2,4,5). If untreated, pain related to critical illness can evolve into chronic pathologic pain observed in 14-77% of ICU survivors (6,7). Patients remember pain long after they leave the ICU (8), with many experiencing post-traumatic stress disorder (9) and ICU-acquired opioid dependence (10). Undertreated pain is also linked to higher mortality rates (11), increased sympathetic stress (12), and decreased tissue oxygen tension, which may lead to poor surgical wound healing and infection (13,14). Consequently, adequate pain control is paramount in the ICU.

Regional techniques are essential to multimodal analgesia in perioperative populations (15). Such techniques offer significant advantages over multimodal pain medications alone, including reduced risk of persistent postoperative pain (16), superior analgesia with lower opioid requirements (17), and fewer side effects with higher patient satisfaction (18). Furthermore, a recent meta-analysis found that regional techniques reduce postoperative neurocognitive dysfunction in major noncardiac surgery (19). Considering the value of regional techniques in perioperative patients, these modalities may represent a promising direction to optimize pain management in critically ill patients, particularly those with post-traumatic or post-surgical presentations.

In this narrative review, we discuss the utility of regional anesthesia for various patient populations in the critical care unit and the challenges faced when performing regional techniques in this high-acuity setting.

Regional Anesthesia for Post-Trauma Patients in the ICU

Trauma represents a significant source of critical illness, making up 46.9% of patients in the ICU, according to a multicenter prevalence study (20). Of these, the most common traumatic injuries were rib fractures at 41.6%, brain injuries at 38.8%, and hemothorax/pneumothorax at 30.8% (20). Most trauma patients report severe pain (21,22). However, pain management in the setting of acute trauma can be complicated by hemodynamic instability, airway compromise, and neurologic injury. Furthermore, systemic opioids can cause sedation and depression of cardiovascular and respiratory functions (23,24), which can worsen a patient's clinical picture and interfere with neurologic exams. As such, regional techniques are especially advantageous in critically ill trauma patients, providing site-specific analgesia with minimal side effects.

Blunt Thoracic Trauma and Rib Fractures

Blunt chest trauma involves injuries ranging from rib fractures, soft tissue contusions, and pneumothoraces (25). Notably, splinting caused by chest wall pain reduces ventilatory effort, which can lead to atelectasis and pneumonia (26). For chest trauma, numerous regional anesthesia techniques can be employed, including thoracic epidural analgesia (TEA), thoracic paravertebral blocks (TPVB), erector spinae plane blocks (ESP), serratus anterior plane blocks (SAP), and intercostal nerve blocks.

In 2016, the Eastern Association for the Surgery of Trauma (EAST) and the Trauma Anesthesiology Society jointly recommended epidurals over non-regional modalities of pain control in blunt thoracic trauma (27). Additionally, two systematic reviews concluded that epidurals provided superior pain relief compared to other modalities in rib fractures (28,29). However, the idea that epidural analgesia is superior to other regional techniques has been challenged by recent meta-analyses, with both Peek et al. (28) and Duch et al. (30) finding no advantages to epidurals over peripheral blocks in terms of mortality, duration of mechanical ventilation, and pulmonary complications. A meta-analysis of 12 studies found peripheral nerve blocks (TPVBs, intercostal, ESP, and SAP) to have better immediate pain control than conventional analgesics, including epidurals (31). A notable randomized controlled trial (RCT) by McKendy et al. (32) reported increased respiratory complications in patients with multiple rib fractures who received epidurals. However, this observational study has a high potential for selection bias due to the cohort-matched group design determined by the clinician's decision to place an epidural or not. Particularly in patients with hemodynamic instability or coagulopathy, other regional modalities may be more appropriate and should be considered. An overview of the indications, benefits, and risks of thoracic regional techniques can be found in Figure 1.

Two recent RCTs support the efficacy of paravertebral blocks for improving pulmonary function parameters in rib fractures (33,34). A scoping review of 37 studies found almost universal improvements in pain and respiratory parameters after ESP blocks in rib fracture patients without complications, even in the setting of anticoagulation and coagulopathy (35). Indeed, RCTs suggest ESP blocks may be as effective as TPVB (36) with lower pain scores compared to intercostal (37) and SAP blocks (38). Independently, the SABRE RCT found clinically meaningful reduction in pain and opioid use with SAP versus standard of care (39). Intercostal blocks with liposomal bupivacaine, while safe, did not improve clinical outcomes (40).

Notably, in geriatric patients, a cohort particularly vulnerable to rib fractures and resultant complications, extensive retrospective studies noted the benefit of early regional intervention to prevent intubation (41) with similar outcomes between TEA and TPVB (42), suggesting further subgroup RCT assessments are needed.

Overall, recent literature on regional techniques in blunt chest trauma remains low quality and heterogeneous, making definitive conclusions regarding the optimal analgesic technique impossible. In fact, by 2023, EAST had changed its previous recommendation for epidurals over systemic modalities due to insufficient evidence of the superiority of epidural or locoregional techniques over other multimodal analgesia. Instead, they suggested providers use their judgment and available resources to provide a multifaceted pain management strategy (43) -a sentiment echoed by Hammal et al. (29) in their updated 2024 systematic review.

Regional Anesthesia for Post-Surgical Patients in the ICU

Around one-third of all critically ill patients worldwide are admitted to surgical ICUs following major elective or emergency surgeries (44,45). Over half of post-surgical ICU patients report pain at maximal intensity with suboptimal pain

control (46). The following section will focus on evidence for the use of regional analgesia for specific subpopulations of post-surgical patients in the ICU.

Extremity Injuries, Surgeries, and Considerations

While traumatic extremity injuries are common, the majority are treated with surgery and will, therefore, be discussed in this section.

Hip fractures tend to occur in patients who are older, more frail, and have more comorbidities than other trauma patients (47). Lumbar epidural analgesia reduces major adverse cardiac events after hip fracture. The American College of Cardiology/American Heart Association (ACC/AHA) recommended epidural consideration for hip fractures in their 2024 guidelines for perioperative cardiovascular management (48). Peripheral blocks are another alternative, and a Cochrane review of peripheral nerve blocks in hip fractures showed reduced pain scores and confusion in patients receiving regional analgesia (49). The innervation to the hip is complex and involves numerous nerves and their articular branches, including the femoral, obturator, and accessory obturator nerves for the anterior capsule. The posterior joint capsule innervation involves the nerve to the quadratus femoris, sciatic, and superior and inferior gluteal nerves (50). These nerves, in addition to the lateral femoral cutaneous (LFCN), ilioinguinal, iliohypogastric, and posterior femoral cutaneous nerves, contribute to skin innervation over standard surgical incisions for hip fractures. Each nerve can be targeted individually or in combination proximally, like femoral and obturator nerve coverage with a lumbar plexus

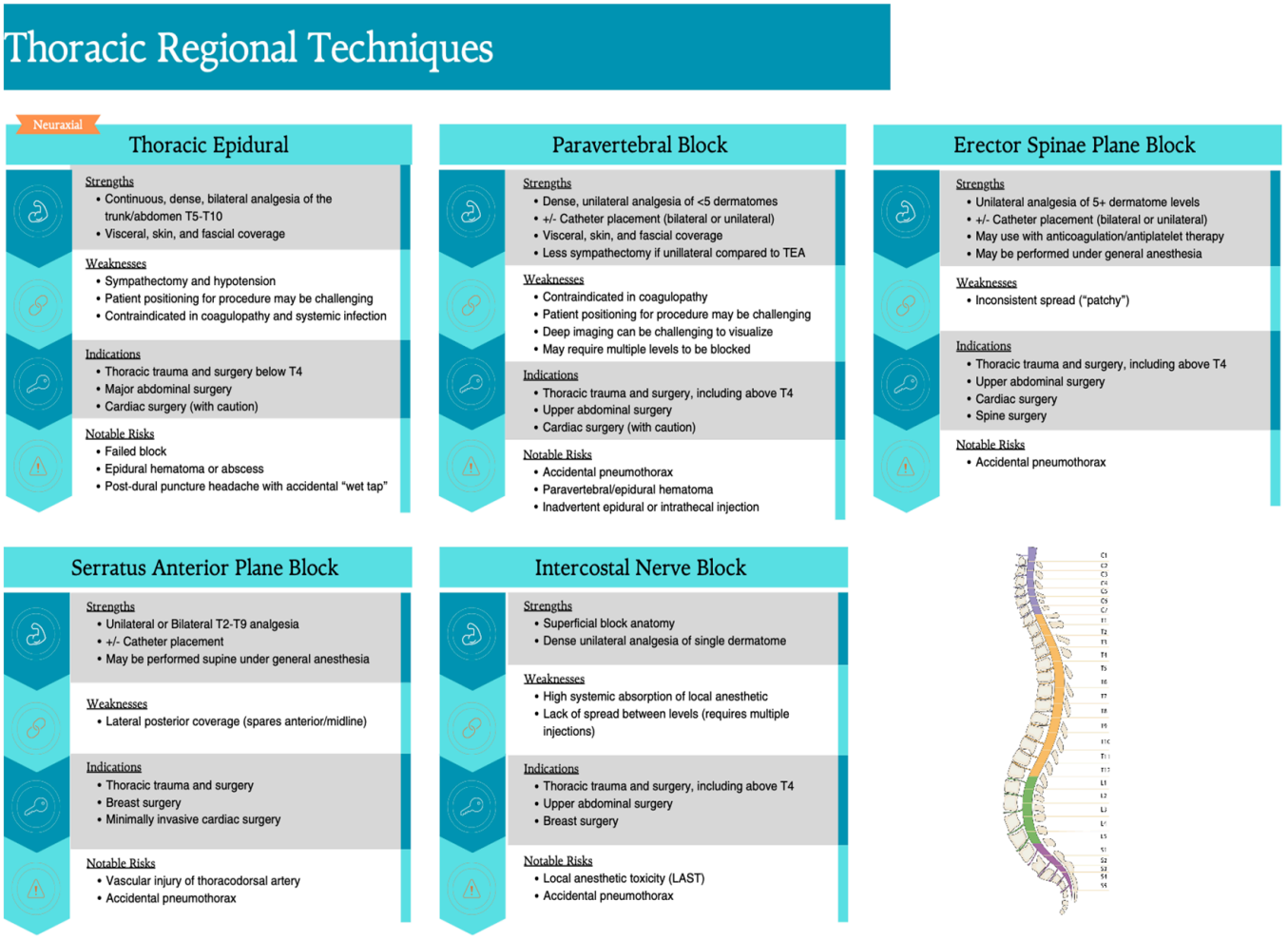

Figure 1. Thoracic regional techniques
Image acknowledgment: dermatomal spine image was obtained from Servier Medical Art, licensed under Creative Commons Attribution 4.0 International (https://creativecommons.org/licenses/by/4.0/). No changes have been made

block. However, newer fascial plane blocks, such as the suprainguinal fascia iliaca and the pericapsular nerve group (PENG), allow multiple nerves to be targeted in a single injection. A multisite RCT found femoral nerve blockade followed by continuous fascia iliaca blocks to provide superior pain scores and walking distances compared to standard systemic therapy in hip fractures (51). Fascia iliaca blockade has been observed to be safe and reliable by a systematic review of 27 RCTs (52). Studies ranging from case series to RCTs support the role of PENG blocks in this fragile patient population (53,54) which may be superior to femoral and fascia iliaca blocks (55,56). There is also evidence of benefit when PENG and fascia iliaca blocks are combined (57). Additional blocks with potential efficacy in this patient population include lumbar quadratus lumborum (QL) and ESP blocks (58).

Other types of extremity fractures warrant different regional techniques. Numerous studies demonstrate a reduction in opioid consumption and improved pain scores when regional anesthesia is utilized for extremity fractures (59-61). For clavicle fractures, superficial or intermediate cervical plexus blocks combined with interscalene blockade is a classic combination for both medial and lateral coverage (62). For upper extremity fractures, brachial plexus blocks may be considered, including interscalene, supraclavicular, infraclavicular, costoclavicular, and axillary approaches, as well as individual axillary or suprascapular nerve blocks (63-65). For lower extremity fractures, clinicians can consider femoral, LFCN, adductor canal saphenous, and nerve to the vastus medialis blockade, obturator, genicular, iPACK, parasacral, subgluteal, or popliteal sciatic nerve, and ankle blocks (66-68). The choice of nerve block technique depends largely on the location of trauma, the need for analgesia alone, or the need for surgical-level anesthesia. A summary of regional techniques for upper and lower extremities may be found in Figure 2 and Figure 3, respectively.

When caring for patients with traumatic extremity injuries, the potential for compartment syndrome must be considered. The most common injuries associated with compartment syndrome in descending order are tibial shaft fractures, soft tissue injuries, and distal radius fractures (69). Controversy exists between anesthesiologists and

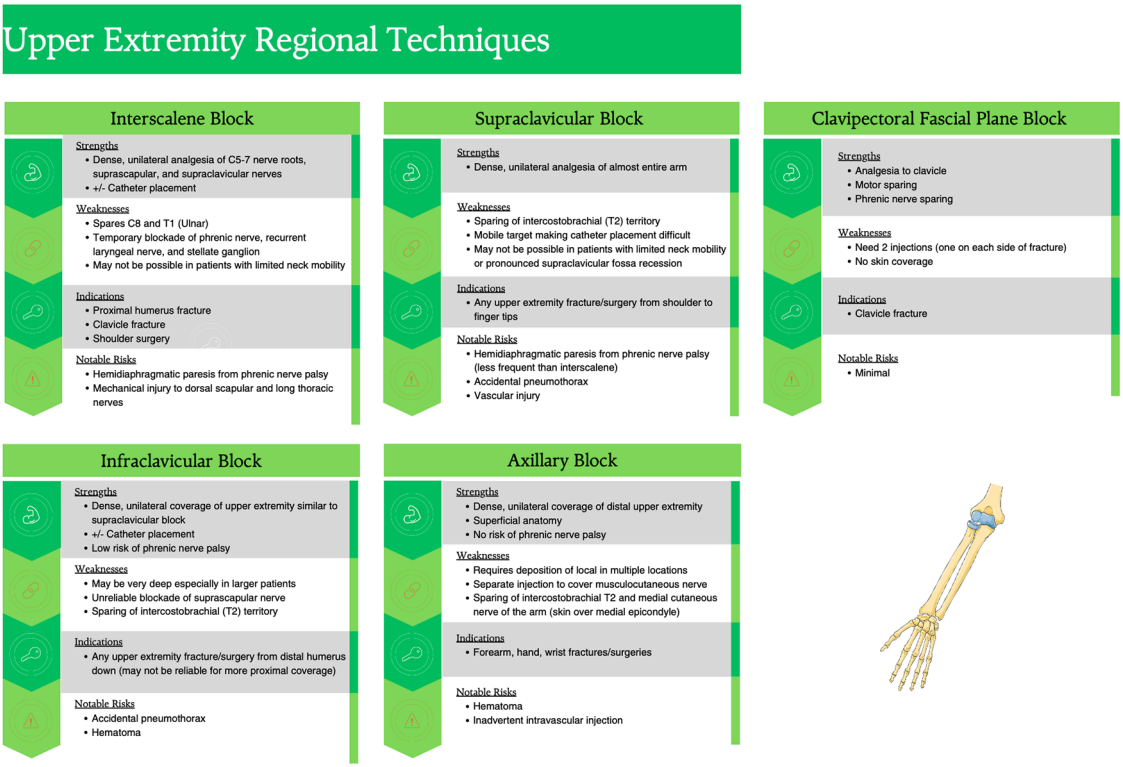

Figure 2. Upper extremity regional techniques
Image acknowledgment: Upper extremity bone image was obtained from Servier Medical Art, licensed under Creative Commons Attribution 4.0 International (https://creativecommons.org/licenses/by/4.0/). No changes have been made

surgeons regarding the potential for regional techniques to delay the diagnosis of this rare but devastating complication by masking one of the earliest clinical signs of compartment syndrome: pain. Unfortunately, the current literature on this subject is not robust and primarily comprises case reports and series. In the last 10 years, there have been two systematic reviews on the subject. Driscoll et al. (70) found that 75% of 34 case reports published since 2009 did not show an increased risk for delayed diagnosis of compartment syndrome following regional anesthesia in orthopedic procedures. Tran et al. (71) found only 6 case reports, 2 of which demonstrated delayed diagnosis of compartment syndrome in the setting of peripheral nerve blockade for long bone fractures. A retrospective study by Cunningham et al. (60) found regional techniques reduced opioid use without incidence of compartment syndrome in tibial plateau fracture. Also notable is a study by Chen et al. (72) in healthy volunteers, which showed regional blocks did decrease ischemic pain but to variable extents, suggesting that regional techniques can be titrated to balance analgesic benefits with the risk of delaying diagnosis. Given the paucity of literature, it is challenging to determine the best analgesic path for patients at risk for compartment syndrome. The European Society of Regional Anaesthesia and Pain Therapy (ESRA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) 2015 joint committee provided evidence-based advice for pediatric patients focusing on low-dose local anesthetics and infusion rates as well as close monitoring when regional anesthesia is used in high-risk patients (73). Unfortunately, no such recommendations exist in adult populations.

Not all traumatic limb injuries result in fractures. Traumatic amputations have increased globally in recent years (74). Adequate pain control in the setting of amputation is critical due to the risk of phantom limb pain, which is estimated to affect 64% of patients (75) and is thought to be caused by cortical reorganization (76). Regional analgesia may play a fundamental role in mitigating the risk of this debilitating chronic condition (77). A multicentered RCT found that continuous nerve catheters doubled the chance of clinically significant improvement of phantom limb pain (78). However, more studies are needed to elucidate the role of regional anesthesia in this population fully.

Thoracic Surgery

There are many studies on regional anesthesia in thoracic surgery. This review will focus on thoracotomies and esophagectomies to reflect the patient population of the ICU. Thoracic surgery is unique in that pulmonary rather than cardiovascular complications account for most morbidity and

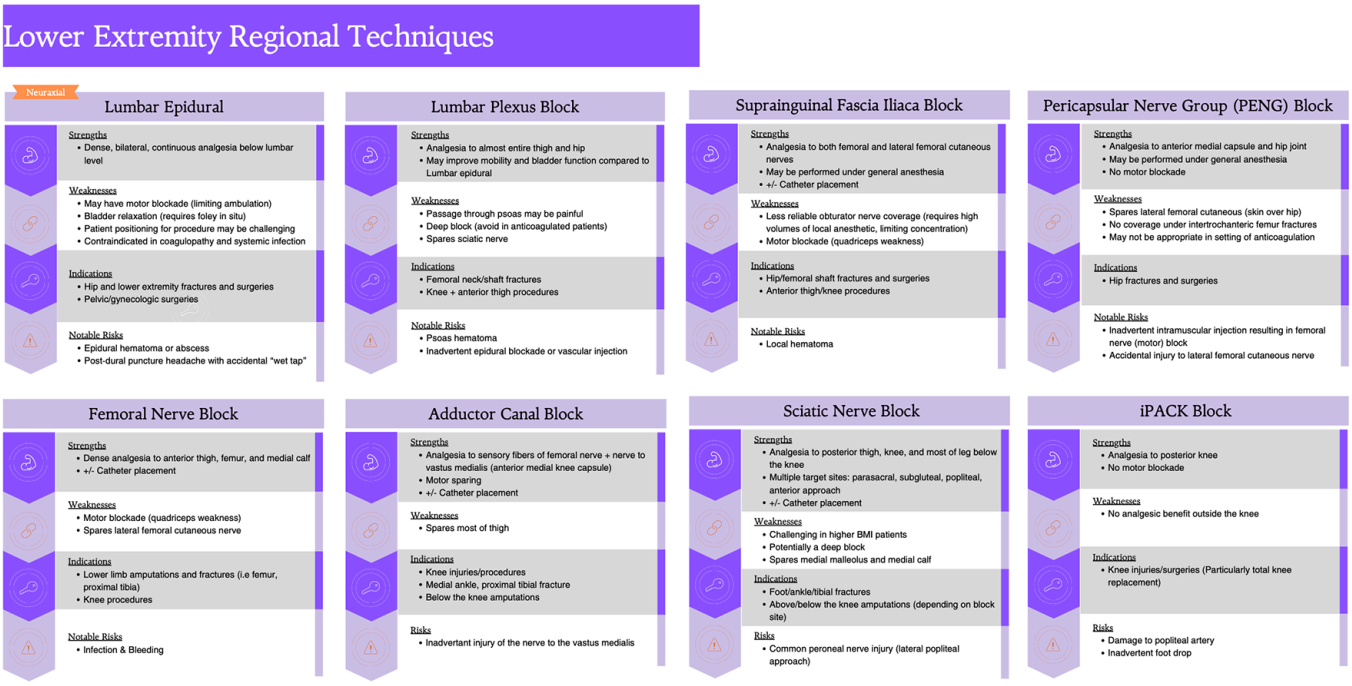

Figure 3. Lower extremity regional techniques

mortality (79). A 2017 meta-analysis showed no differences in postoperative pulmonary complications (PPCs) or pain scores between systemic and epidural analgesia or systemic and paravertebral analgesia after esophagectomy. Still, the interpretation is limited by their inclusion of studies that were not high-level RCTs (80). A more stringent 2020 meta-analysis of 2494 patients found low-quality evidence that epidurals reduce the risk of PPCs in patients undergoing major abdominal and thoracic surgery (81). Most recently, a 2024 meta-analysis found a similar reduction of PPCs and better pain reduction associated with epidurals after esophagectomy (82). Other systematic reviews have shown regional techniques can reduce persistent postoperative pain (83) and reduce opioid consumption (84) after thoracic surgeries.

Numerous systematic reviews demonstrate equal analgesic efficacy of paravertebral blocks to epidurals with a lower risk of complications (85-87). Another meta-analysis found TPVBs were superior to ESP for postoperative analgesia after thoracic surgery (88). Even so, two meta-analyses found postoperative pain control benefits from ESP blocks (89,90). Recent systematic reviews have also shown intercostal blocks to be non-inferior to TPVBs and TEAs (91) and found SAPs to provide effective analgesia in the thoracic surgical population (92-94). Generally, the same variety of regional techniques may be employed for thoracic surgery as for thoracic trauma (as listed in Figure 1), and it is up to the clinician to determine which technique is best on a case-by-case basis.

Patients receiving lung transplants make up a notable population of thoracic surgical patients. TEA is the touchstone for analgesia after lung transplant surgery, though few studies are available in this population. Preoperative TEA is associated with better pain control, lower opioid use, and shorter duration of mechanical ventilation and ICU stay (95). However, TEA must be used cautiously in this population, which may require anticoagulation for extracorporeal membrane oxygenation in the perioperative period (96). Two small studies have also found paravertebral catheters effective (97,98).

Major Abdominal and Vascular Surgery

TEA is the gold standard for postoperative pain relief after major abdominal surgery (99-101). The 2024 ACC/AHA guidelines recommend thoracic epidurals for major abdominal surgery based on moderate evidence supporting a decreased risk of major adverse cardiovascular events (48).

In open abdominal aortic aneurysm repairs, combined TEA and general anesthesia are associated with reduced mortality, myocardial ischemia, postoperative bowel ischemia, and pulmonary complications (102). The use of TEA in thoraco-abdominal aortic aneurysm repair is associated with better postoperative pain control and lower in-hospital length of stay (103). A Cochrane review of 15 RCTs showed that postoperative epidural analgesia led to better pain management in the first 3 days by Visual Analog Scale scores, earlier tracheal extubation, and lower incidence of myocardial ischemia in this same population (104) However, it is prudent to consider that these studies included primarily trials conducted before 2000, before the availability of endovascular techniques. The impact of TEA on mortality and pulmonary and cardiac complications was not supported by a recent retrospective review of 2,145 patients who underwent aortic aneurysm repair between 2014 and 2016 and found that epidurals were correlated with higher transfusion requirements (105).

TEA is associated with failure rates as high as 32% (106) and hypotension (107). Additionally, an indwelling catheter is undesirable in a coagulopathic or septic patient, both of which are occasional complications after extensive abdominal surgery. Thus, other effective regional techniques may be considered for major abdominal and vascular surgeries, including paravertebral (108,109) and erector spinae catheters (110). Paravertebral catheters are likely to be most effective in the case of abdominal aortic aneurysm repair via retroperitoneal approach and have reduced risk of hypotension (108). Fascial plane blocks offer alternatives to TEA. While evidence for fascial plane blocks in the ICU population specifically is lacking, these blocks have been studied extensively in major abdominal surgery, specifically-transversus abdominis plane (TAP), erector spinae plane (ESP), QL, and rectus sheath blocks. Of these, ESP and QL blocks can provide some visceral analgesia due to the spread of local anesthetic to the paravertebral space, but this effect is inconsistent (111). Compared to TEA, studies on fascial plane blocks have demonstrated mixed results. While some studies found TAP blocks to be non-inferior to TEA, others show TEA patients to have lower opioid requirements and pain scores postoperatively (101,112). Nevertheless, there is consistent evidence that fascial plane blocks effectively decrease the need for postoperative opioids and lower pain scores in comparison to placebo (101,111,112). The choice between blocks depends on the surgery and placement of

incisions and drains. For example, while rectus sheath blocks are effective for midline incisions, TAP and QL blocks work well for lateral and transverse incisions. A description of abdominal wall regional techniques may be found in Figure 4.

Liver transplant surgery should be considered separately regarding candidacy for regional techniques. Liver transplant recipients have less postoperative pain compared to other major abdominal surgeries, potentially due to denervation of the donor liver, reduced abdominal distention after drainage of ascites, and increased plasma levels of endogenous neuropeptides (113). Even so, liver transplant patients do experience significant postoperative pain and should be provided adequate analgesia. Coagulopathy and thrombocytopenia, often present in these patients, are a contraindication to epidural placement. Additionally, a recent retrospective study of 685 liver transplant patients found preoperative TEA to provide minimal differences in pain scores (Numerical Rating score of 1.4 vs 1.8) compared to

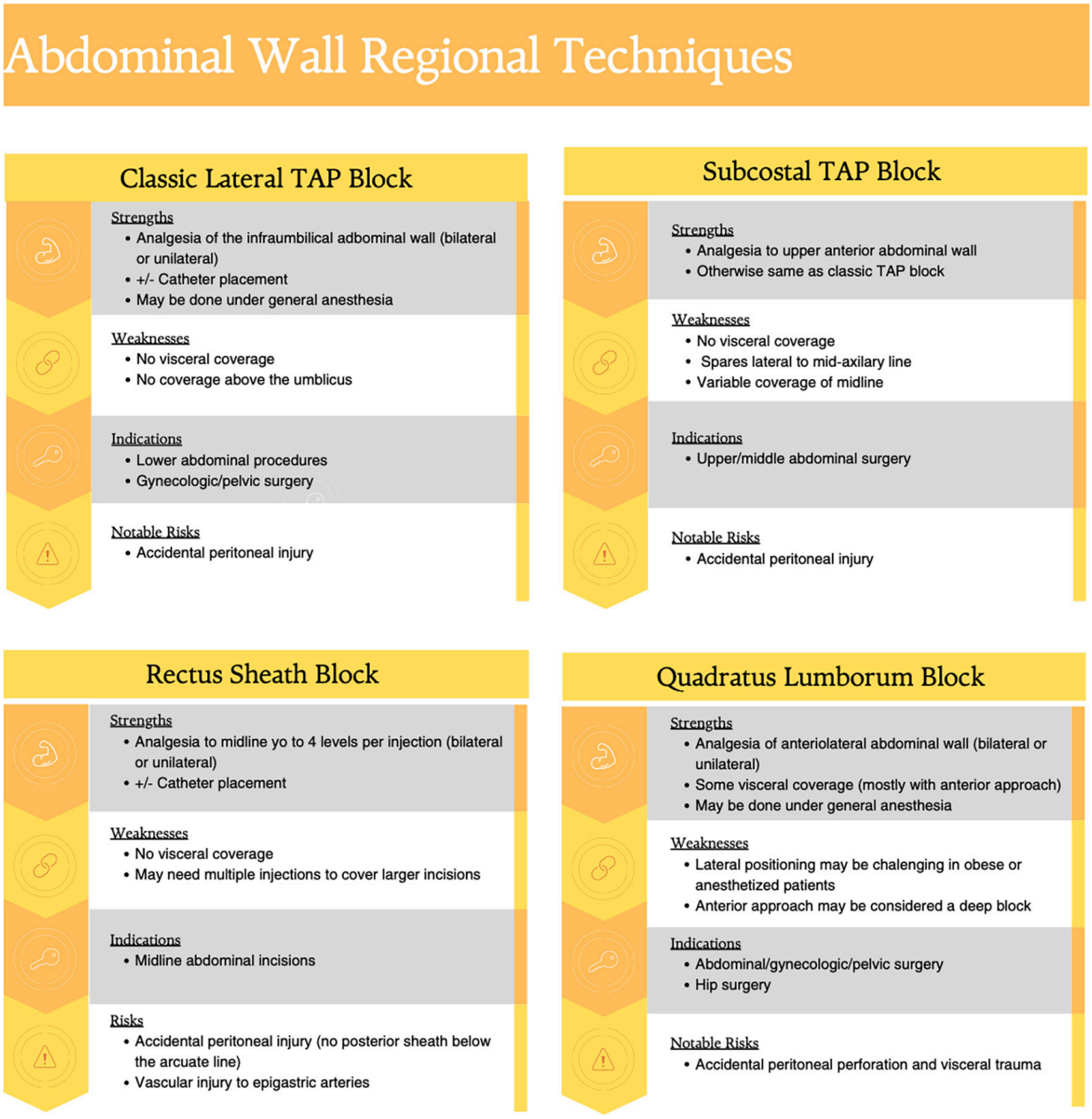

Figure 4. Abdominal wall regional techniques

patients without TEA (114). However, TEA is an effective mode of pain relief after open liver resection, including for donor liver resection, and has been shown to decrease opioid consumption in the postoperative period (115). Paravertebral catheters and single-shot blocks have also been effective, though pain control is inferior to TEA (115,116). TAP catheters and blocks are also an effective modality but have not been compared head to head with TEAs or PVBs (115,116).

Cardiac Surgery

We will briefly mention the utility of regional analgesia in cardiovascular surgical patients as they tend to present to subspecialty ICUs. Patients undergoing open heart surgery frequently require anticoagulation for cardiopulmonary bypass, which makes the use of TEA controversial. A Cochrane review concluded that TEA reduced pain scores by 1 point on a scale of 0 to 10, decreased the length of mechanical ventilation by 2.4 hours, and decreased the rate of myocardial infarction, atrial fibrillation, and respiratory depression at 30 days post-cardiac surgery (117). However, the evidence in this study was of low quality overall, and there was insufficient data to comment on the incidence of epidural hematoma. Based on mathematical modeling, the incidence of spinal injury from epidural hematoma is estimated between 1:150,000 and 1:1,500 for epidurals in conventional cardiac surgery (118). Of note, the 2018 ASRA guidelines state that there is insufficient evidence for an increased risk of epidural hematoma in the setting of cardiopulmonary bypass (119). Meanwhile, paravertebral blocks have been used increasingly for cardiac surgery, particularly in minimally invasive procedures performed via lateral thoracotomy (120). Paravertebral catheters placed perioperatively decrease intraoperative opioid use, reduce nausea and vomiting, and shorten the length of mechanical ventilation with minimal hypotension (121,122). In this patient population, it is essential to remember that paravertebral blocks are still considered a deep block, which puts them at higher risk in the setting of anticoagulation.

Limitations in Clinical Practice

Sedation

The prevalence of sedation among ICU patients presents a challenge to the performance of regional techniques. Light to moderate sedation, which maintains meaningful contact with the patient, is generally beneficial by providing anxiolysis and increasing patient tolerance of regional nerve blockade (123). However, controversy exists regarding the safety of performing regional blocks on patients under deep sedation or general anesthesia, which obliterates feedback from the patient regarding periprocedural paresthesias and signs or symptoms of local anesthetic toxicity. Many assert that it is necessary for patients to be awake and cooperative enough to communicate when there is pain or paresthesia during a nerve block to protect against neural injury. This concern mainly applies to blocks targeted directly at a nerve versus fascial plane techniques, which are considered safe even under general anesthesia due to the lower risk of nerve damage (124). Indeed, ASRA recommends against regional techniques in heavily sedated or anesthetized patients unless the benefit clearly outweighs the risk (125). Even so, there is little evidence that pain or paresthesia predicts neural injury (126). In fact, regional techniques are routinely used safely in anesthetized pediatric patients. A study by the Pediatric Regional Anesthesia Network of over 100,000 blocks found no incidence of permanent neurologic deficits (127). A prospective study in sedated and mechanically ventilated trauma patients concluded that continuous regional anesthesia seems safe in the setting of heavy sedation-although with 76 patients analyzed, it was underpowered to see significant differences in outcomes (128). As such, the decision to perform regional techniques in heavily sedated patients in the ICU should be considered on a case-by-case basis with careful assessment of the risk-to-benefit ratio. Of note, the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Panel within the Society of Critical Care Medicine Congress strengthened their recommendation of light versus deep sedation in the management of critically ill patients, therefore in many cases this obstacle to providing regional anesthesia may lessen (129).

Sepsis and Infection

ICU patients frequently have pre-existing or nosocomial infections (130). Puncture site infection is an absolute contraindication to any regional technique. Systemic infection is often considered a relative contraindication to regional anesthesia due to concerns about seeding infection into fascial planes, nerves, or the neuraxial space, especially in the setting of indwelling catheters. A recent systematic review across various patient populations found that the incidence of infectious complications for central neuraxial blockade was 9/100,000 and 1.8% in peripheral nerve catheters (131). Recent studies show a low incidence of central nervous system infection after neuraxial techniques in patients at risk for or with active bacteremia in the acute

perioperative period (132). However, ICU admission is a risk factor for infection of peripheral nerve catheters (133), especially if they are in situ for over 48 hours (134). Factors that may reduce the risk of infection include prophylactic antibiotics (135) and tunneling of catheters (136). The risk of infection must be weighed against the benefits of regional techniques. Any indwelling catheters should be removed as early as is reasonable to minimize colonization while preserving maximal analgesic benefit.

Coagulopathies

Many patients in the ICU experience coagulopathies of various etiologies due to sepsis or trauma (137,138). Additionally, the use of anticoagulants and antiplatelet medication is expanding. Thus, clinicians must weigh the risks of regional anesthesia in patients susceptible to bleeding. ESRA and ASRA have guidelines for time intervals after cessation of antiplatelet and anticoagulant therapies before performing regional and neuraxial techniques (119,139). Bleeding complications following peripheral nerve blocks in patients on antiplatelet and anticoagulant medications are rare, estimated to be less than 1% (140). When weighing the risks for hematoma in coagulopathic patients, it is crucial to consider the depth and compressibility of the site for each regional technique. Neuraxial techniques have the highest relative risk followed in descending order of risk by deep blocks such as deep lumbar plexus, proximal sciatic, and infraclavicular blocks, in addition to perivascular blocks such as femoral or axillary blocks, then fascial plane blocks (141). Although controversial, many practitioners feel perineural catheters have a higher risk for bleeding, given they require a larger, blunt tip needle for placement, and there is an additional risk with catheter removal or dislodgement (142).

Hemodynamic Instability

Hemodynamic instability is a common concern in the critically ill, estimated to affect 19% of patients in the ICU (143). The cardiovascular stability of a patient must be considered in the context of regional analgesic techniques. Specifically, neuraxial techniques, such as epidurals and spinals, are associated with hypotension and bradycardia in the setting of sympathetic blockade (144,145). As such, neuraxial analgesia may be best avoided in patients already at significant risk for hemodynamic compromise or already on vasopressor support. Consideration of shifting from a local anesthetic epidural infusion to solely an opioid infusion, such as fentanyl, may decrease hypotension (146,147). Even single-sided TVPB may decrease the total local anesthetic spread to the spinal sympathetic chain, lessening the risk of hypotension (85,87,108,148). On the other hand, peripheral nerve blockade may be beneficial in tenuous patients by avoiding the use of sedation medications, which can also compromise cardiovascular stability (149). For example, superficial cervical plexus blockade can facilitate awake central line cannulation (150) and intercostal block may be used for chest tube placement (151).

Conclusion

For patients in the ICU, pain is a prominent concern often associated with long-term consequences. Regional techniques offer targeted analgesia, generally without systemic side effects. From rib fractures and limb fractures to major surgeries, there is a clear benefit to regional analgesia among critically ill patients. However, current literature is insufficient to determine the best technique for optimal pain control in every case. As such, each patient should be evaluated carefully to determine their candidacy for regional analgesia versus systemic pain management alone. Hemodynamic status, infection, level of sedation, and site of surgery or injury are all factors to consider when choosing the best regional modality for each patient.

Ethics

Footnotes

Authorship Contributions

Concept: M.A.B., K.M.J., Design: M.A.B., K.M.J., Analysis or Interpretation: L.H., M.A.B., K.M.J., Literature Search: L.H., M.A.B., K.M.J., Writing: L.H., M.A.B., K.M.J.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Chanques G, Sebbane M, Barbotte E, Viel E, Eledjam JJ, Jaber S. A prospective study of pain at rest: incidence and characteristics of an unrecognized symptom in surgical and trauma versus medical intensive care unit patients. Anesthesiology. 2007;107:858-60.
2. Desbiens NA, Wu AW, Broste SK, Wenger NS, Connors AF Jr, Lynn J, et al. Pain and satisfaction with pain control in seriously ill hospitalized adults: findings from the SUPPORT research investigations. For the SUPPORT investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatmentm. Crit Care Med. 1996;24:1953-61.
3. Gélinas C. Management of pain in cardiac surgery ICU patients: have we improved over time? Intensive Crit Care Nurs. 2007;23:298-303.
4. Bertolini G, Minelli C, Latronico N, Cattaneo A, Mura G, Melotti RM, et al. The use of analgesic drugs in postoperative patients: the neglected problem of pain control in intensive care units. An observational, prospective, multicenter study in 128 Italian intensive care units. Eur J Clin Pharmacol. 2002;58:73-7.
5. Alderson SM, McKechnie SR. Unrecognised, undertreated, pain in ICU—Causes, effects, and how to do better. Open J Nurs. 2013;03:108–13.
6. Kemp HI, Laycock H, Costello A, Brett SJ. Chronic pain in critical care survivors: a narrative review. Br J Anaesth. 2019;123:e372-e384.
7. Mäkinen OJ, Bäcklund ME, Liisanantti J, Peltomaa M, Karlsson S, Kalliomäki ML. Persistent pain in intensive care survivors: a systematic review. Br J Anaesth. 2020;125:149-58.
8. Puntillo KA, Max A, Chaize M, Chanques G, Azoulay E. Patient Recollection of ICU Procedural Pain and Post ICU Burden: The Memory Study. Crit Care Med. 2016;44:1988-95.
9. Granja C, Gomes E, Amaro A, Ribeiro O, Jones C, Carneiro A, et al. Understanding posttraumatic stress disorder-related symptoms after critical care: the early illness amnesia hypothesis. Crit Care Med. 2008;36:2801-9.
10. Puntillo KA, Naidu R. Chronic pain disorders after critical illness and ICU-acquired opioid dependence: two clinical conundra. Curr Opin Crit Care. 2016;22:506-12.
11. Yamashita A, Yamasaki M, Matsuyama H, Amaya F. Risk factors and prognosis of pain events during mechanical ventilation: a retrospective study. J Intensive Care. 2017;5:17.
12. Burton AR, Fazalbhoy A, Macefield VG. Sympathetic Responses to Noxious Stimulation of Muscle and Skin. Front Neurol. 2016;7:109.
13. Akça O, Melischek M, Scheck T, Hellwagner K, Arkiliç CF, Kurz A, et al. Postoperative pain and subcutaneous oxygen tension. Lancet. 1999;354:41-2.
14. Buggy DJ, Doherty WL, Hart EM, Pallett EJ. Postoperative wound oxygen tension with epidural or intravenous analgesia: a prospective, randomized, single-blind clinical trial. Anesthesiology. 2002;97:952-8.
15. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17:131-57.
16. Weinstein EJ, Levene JL, Cohen MS, Andreae DA, Chao JY, Johnson M, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev. 2018;4:CD007105.
17. Richman JM, Liu SS, Courpas G, Wong R, Rowlingson AJ, McGready J, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg. 2006;102:248-57.
18. Kumar K, Kirksey MA, Duong S, Wu CL. A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively. Anesth Analg. 2017;125:1749-60.
19. Singh NP, Makkar JK, Borle A, Singh PM. Role of supplemental regional blocks on postoperative neurocognitive dysfunction after major non-cardiac surgeries: a systematic review and meta-analysis of randomized controlled trials. Reg Anesth Pain Med. 2024;49:49-58.
20. Michetti CP, Fakhry SM, Brasel K, Martin ND, Teicher EJ, Newcomb A, et al. Trauma ICU Prevalence Project: the diversity of surgical critical care. Trauma Surg Acute Care Open. 2019;4:e000288.
21. Kejela S, Seyoum N. Acute pain management in the trauma patient population: are we doing enough? A prospective observational study. J Trauma Inj. 2022;35:151-8.
22. Berben SA, Meijs TH, van Dongen RT, van Vugt AB, Vloet LC, Mintjes-de Groot JJ, et al. Pain prevalence and pain relief in trauma patients in the Accident & Emergency department. Injury. 2008;39:578-85.
23. Paul AK, Smith CM, Rahmatullah M, Nissapatorn V, Wilairatana P, Spetea M, et al. Opioid Analgesia and Opioid-Induced Adverse Effects: A Review. Pharmaceuticals (Basel). 2021;14:1091.
24. Krantz MJ, Palmer RB, Haigney MCP. Cardiovascular Complications of Opioid Use: JACC State-of-the-Art Review. J Am Coll Cardiol. 2021;77:205-23.
25. Dogrul BN, Kiliccalan I, Asci ES, Peker SC. Blunt trauma related chest wall and pulmonary injuries: An overview. Chin J Traumatol. 2020;23:125-38.
26. May L, Hillermann C, Patil S. Rib fracture management. BJA Educ. 2016 Jan;16(1):26–32.
27. Galvagno SM Jr, Smith CE, Varon AJ, Hasenboehler EA, Sultan S, Shaefer G, et al. Pain management for blunt thoracic trauma: A joint practice management guideline from the Eastern Association for the Surgery of Trauma and Trauma Anesthesiology Society. J Trauma Acute Care Surg. 2016;81:936-51.
28. Peek J, Smeeing DPJ, Hietbrink F, Houwert RM, Marsman M, de Jong MB. Comparison of analgesic interventions for traumatic rib fractures: a systematic review and meta-analysis. Eur J Trauma Emerg Surg. 2019;45:597-622.
29. Hammal F, Chiu C, Kung JY, Bradley N, Dillane D. Pain management for hospitalized patients with rib fractures: A systematic review of randomized clinical trials. J Clin Anesth. 2024;92:111276.
30. Duch P, Møller MH. Epidural analgesia in patients with traumatic rib fractures: a systematic review of randomised controlled trials. Acta Anaesthesiol Scand. 2015;59:698-709.
31. Xiao DL, Xi JW. Efficacy of peripheral nerve blocks for pain management in patients with rib fractures: A systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2023;27:899-910.
32. McKendy KM, Lee LF, Boulva K, Deckelbaum DL, Mulder DS, Razek TS, et al. Epidural analgesia for traumatic rib fractures is associated with worse outcomes: a matched analysis. J Surg Res. 2017;214:117-23.
33. Ge YY, Wang XZ, Yuan N, Yuan LY, Ma WH, Hu Y. [Effect of ultrasound guided patient-controlled paravertebral block on pulmonary function in patients with multiple fractured ribs]. Zhonghua Wai Ke Za Zhi. 2016;54:924-8.
34. Yeying G, Liyong Y, Yuebo C, Yu Z, Guangao Y, Weihu M, et al. Thoracic paravertebral block versus intravenous patient-controlled analgesia for pain treatment in patients with multiple rib fractures. J Int Med Res. 2017;45:2085-91.

35. Jiang M, Peri V, Ou Yang B, Chang J, Hacking D. Erector Spinae Plane Block as an Analgesic Intervention in Acute Rib Fractures: A Scoping Review. Local Reg Anesth. 2023;16:81-90.
36. Elawamy A, Morsy MR, Ahmed MAY. Comparison of Thoracic Erector Spinae Plane Block With Thoracic Paravertebral Block for Pain Management in Patients With Unilateral Multiple Fractured Ribs. Pain Physician. 2022;25:483-90.
37. Armin E, Movahedi M, Najafzadeh MJ, Honarmand A, Rukerd MRZ, Mirafzal A. COMPARISON OF ULTRASOUND-GUIDED ERECTOR SPINAE PLANE BLOCK WITH INTERCOSTAL NERVE BLOCK FOR TRAUMA-ASSOCIATED CHEST WALL PAIN. J Emerg Med. 2022;63:520-7.
38. El Malla DA, Helal RAEF, Zidan TAM, El Mourad MB. The Effect of Erector Spinae Block versus Serratus Plane Block on Pain Scores and Diaphragmatic Excursion in Multiple Rib Fractures. A Prospective Randomized Trial. Pain Med. 2022;23:448-55.
39. Partyka C, Asha S, Berry M, Ferguson I, Burns B, Tsacalos K, et al. Serratus Anterior Plane Blocks for Early Rib Fracture Pain Management: The SABRE Randomized Clinical Trial. JAMA Surg. 2024;159:810-7.
40. Wallen TE, Singer KE, Makley AT, Athota KP, Janowak CF, Hanseman D, et al. Intercostal liposomal bupivacaine injection for rib fractures: A prospective randomized controlled trial. J Trauma Acute Care Surg. 2022;92:266-76.
41. Proaño-Zamudio JA, Argandykov D, Renne A, Gebran A, Ouwerkerk JJJ, Dorken-Gallastegi A, et al. Timing of regional analgesia in elderly patients with blunt chest-wall injury. Surgery. 2023;174:901-6.
42. Alizai Q, Arif MS, Colosimo C, Hosseinpour H, Spencer AL, Bhogadi SK, et al. Beyond the short-term relief: Outcomes of geriatric rib fracture patients receiving paravertebral nerve blocks and epidural analgesia. Injury. 2024;55:111184.
43. Mukherjee K, Schubl SD, Tominaga G, Cantrell S, Kim B, Haines KL, et al. Non-surgical management and analgesia strategies for older adults with multiple rib fractures: A systematic review, meta-analysis, and joint practice management guideline from the Eastern Association for the Surgery of Trauma and the Chest Wall Injury Society. J Trauma Acute Care Surg. 2023;94:398-407.
44. Wunsch H, Gershengorn HB, Cooke CR, Guerra C, Angus DC, Rowe JW, et al. Use of Intensive Care Services for Medicare Beneficiaries Undergoing Major Surgical Procedures. Anesthesiology. 2016;124:899-907.
45. Abebe K, Negasa T, Argaw F. Surgical Admissions and Treatment Outcomes at a Tertiary Hospital Intensive Care Unit in Ethiopia: A Two-Year Review. Ethiop J Health Sci. 2020;30:725-32.
46. Ranjeva S, Khoudary A, Kaafarani H, Prout L, Nagrebetsky A, Deng H. 123: Postoperative pain in the ICU: A retrospective cohort study on severity and frequency of assessment. Crit Care Med. 2023 Jan;51(1):44–44.
47. Mathew A, Lukachan GA, Varughese D, Raju N, Mathai AS, Johnson AS. Impact of frailty and comorbidity index on postoperative complications and functional outcomes among elderly patients undergoing hip fracture surgeries under regional anesthesia techniques. Anaesth Pain Intensive Care. 2023 Apr 25;27(2):161–9.
48. Thompson A, Fleischmann KE, Smilowitz NR, de Las Fuentes L, Mukherjee D, Aggarwal NR, et al. 2024 AHA/ACC/ACS/ASNC/HRS/SCA/SCCT/SCMR/SVM Guideline for Perioperative Cardiovascular Management for Noncardiac Surgery: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;150:e351-e442.
49. Guay J, Kopp S. Peripheral nerve blocks for hip fractures in adults. Cochrane Database Syst Rev. 2020;11:CD001159.
50. Laumonerie P, Dalmas Y, Tibbo ME, Robert S, Durant T, Caste T, et al. Sensory Innervation of the Hip Joint and Referred Pain: A Systematic Review of the Literature. Pain Med. 2021;22:1149-57.
51. Morrison RS, Dickman E, Hwang U, Akhtar S, Ferguson T, Huang J, et al. Regional Nerve Blocks Improve Pain and Functional Outcomes in Hip Fracture: A Randomized Controlled Trial. J Am Geriatr Soc. 2016;64:2433-9.
52. Wan HY, Li SY, Ji W, Yu B, Jiang N. Fascia Iliaca Compartment Block for Perioperative Pain Management of Geriatric Patients with Hip Fractures: A Systematic Review of Randomized Controlled Trials. Pain Res Manag. 2020;2020:8503963.
53. Del Buono R, Padua E, Pascarella G, Soare CG, Barbara E. Continuous PENG block for hip fracture: a case series. Reg Anesth Pain Med. 2020;45:835-8.
54. Acharya U, Lamsal R. Pericapsular Nerve Group Block: An Excellent Option for Analgesia for Positional Pain in Hip Fractures. Case Rep Anesthesiol. 2020;2020:1830136.
55. Lin DY, Morrison C, Brown B, Saies AA, Pawar R, Vermeulen M, et al. Pericapsular nerve group (PENG) block provides improved short-term analgesia compared with the femoral nerve block in hip fracture surgery: a single-center double-blinded randomized comparative trial. Reg Anesth Pain Med. 2021;46:398-403.
56. Mosaffa F, Taheri M, Manafi Rasi A, Samadpour H, Memary E, Mirkheshti A. Comparison of pericapsular nerve group (PENG) block with fascia iliaca compartment block (FICB) for pain control in hip fractures: A double-blind prospective randomized controlled clinical trial. Orthop Traumatol Surg Res. 2022;108:103135.
57. Desai DJ, Shah N, Bumiya P. Combining Pericapsular Nerve Group (PENG) Block With the Supra-Inguinal Fascia Iliaca Block (SIFICB) for Perioperative Analgesia and Functional Recovery in Patients Undergoing Hip Surgeries: A Retrospective Case Series. Cureus. 2023;15:e36374.
58. Dangle J, Kukreja P, Kalagara H. Review of current practices of peripheral nerve blocks for hip fracture and surgery. Curr Anesthesiol Rep. 2020;10:259–66.
59. Cunningham DJ, LaRose MA, Zhang GX, Au S, MacAlpine EM, Paniagua AR, et al. Regional anesthesia reduces inpatient and outpatient perioperative opioid demand in periarticular elbow surgery. J Shoulder Elbow Surg. 2022;31:e48-e57.
60. Cunningham DJ, LaRose M, Zhang G, Patel P, Paniagua A, Gadsden J, et al. Regional Anesthesia Associated With Decreased Inpatient and Outpatient Opioid Demand in Tibial Plateau Fracture Surgery. Anesth Analg. 2022;134:1072-81.
61. Lantieri MA, Novicoff WM, Yarboro SR. Regional anesthesia provides limited decreases in opioid use following distal tibia and ankle fracture surgery. Eur J Orthop Surg Traumatol. 2023;33:2633–8.
62. Lee CCM, Beh ZY, Lua CB, Peng K, Fathil SM, Hou JD, Lin JA. Regional Anesthetic and Analgesic Techniques for Clavicle Fractures and Clavicle Surgeries: Part 1-A Scoping Review. Healthcare (Basel). 2022;10:1487.
63. Neal JM, Gerancher JC, Hebl JR, Ilfeld BM, McCartney CJ, Franco CD, Hogan QH. Upper extremity regional anesthesia: essentials of our current understanding, 2008. Reg Anesth Pain Med. 2009;34:134-70.
64. Li JW, Songthamwat B, Samy W, Sala-Blanch X, Karmakar MK. Ultrasound-Guided Costoclavicular Brachial Plexus Block: Sonoanatomy, Technique, and Block Dynamics. Reg Anesth Pain Med. 2017;42:233-40.

65. Dhir S, Sondekoppam RV, Sharma R, Ganapathy S, Athwal GS. A Comparison of Combined Suprascapular and Axillary Nerve Blocks to Interscalene Nerve Block for Analgesia in Arthroscopic Shoulder Surgery: An Equivalence Study. Reg Anesth Pain Med. 2016;41:564-71.
66. Akesen S, Akesen B, Atıcı T, Gurbet A, Ermutlu C, Özyalçın A. Comparison of efficacy between the genicular nerve block and the popliteal artery and the capsule of the posterior knee (IPACK) block for total knee replacement surgery: A prospective randomized controlled study. Acta Orthop Traumatol Turc. 2021;55:134-40.
67. Chan E, Howle R, Onwochei D, Desai N. Infiltration between the popliteal artery and the capsule of the knee (IPACK) block in knee surgery: a narrative review. Reg Anesth Pain Med. 2021;46:784-805.
68. Kang C, Hwang DS, Song JH, Lee GS, Lee JK, Hwang SJ, et al. Clinical analyses of ultrasound-guided nerve block in lower-extremity surgery: A retrospective study. J Orthop Surg (Hong Kong). 2021;29:2309499021989102.
69. von Keudell AG, Weaver MJ, Appleton PT, Bae DS, Dyer GSM, Heng M, et al. Diagnosis and treatment of acute extremity compartment syndrome. Lancet. 2015;386:1299–310.
70. Driscoll EB, Maleki AH, Jahromi L, Hermecz BN, Nelson LE, Vetter IL, et al. Regional anesthesia or patient-controlled analgesia and compartment syndrome in orthopedic surgical procedures: a systematic review. Local Reg Anesth. 2016;9:65–81.
71. Tran AA, Lee D, Fassihi SC, Smith E, Lee R, Siram G. A systematic review of the effect of regional anesthesia on diagnosis and management of acute compartment syndrome in long bone fractures. Eur J Trauma Emerg Surg. 2020;46:1281–90.
72. Chen Y-YK, Lirk P, Flowers KM, Colebaugh CA, Wilson JM, Zeballos J, et al. Impact of varying degrees of peripheral nerve blockade on experimental pressure and ischemic pain: adductor canal and sciatic nerve blocks in a human model of compartment syndrome pain. Reg Anesth Pain Med. 2022;47:630–6.
73. Ivani G, Suresh S, Ecoffey C, Bosenberg A, Lonnqvist P-A, Krane E, et al. The European Society of Regional Anaesthesia and Pain Therapy and the American Society of Regional Anesthesia and Pain Medicine joint committee practice advisory on controversial topics in pediatric Regional Anesthesia. Reg Anesth Pain Med. 2015;40:526–32.
74. Yuan B, Hu D, Gu S, Xiao S, Song F. The global burden of traumatic amputation in 204 countries and territories. Front Public Health. 2023;11:1258853.
75. Limakatso K, Bedwell GJ, Madden VJ, Parker R. The prevalence and risk factors for phantom limb pain in people with amputations: A systematic review and meta-analysis. PLoS One. 2020;15:e0240431.
76. Birbaumer N, Lutzenberger W, Montoya P, Larbig W, Unertl K, Töpfner S, et al. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci. 1997;17:5503–8.
77. Kukreja P, Paul LM, Sellers AR, Nagi P, Kalagara H. The role of regional anesthesia in the development of chronic pain: A review of literature. Curr Anesthesiol Rep. 2022;12:417–38.
78. Ilfeld BM, Khatibi B, Maheshwari K, Madison S, Ali Sakr Esa W, Mariano ER, et al. Patient-centered results from a multicenter study of continuous peripheral nerve blocks and postamputation phantom and residual limb pain: secondary outcomes from a randomized, clinical trial. Reg Anesth Pain Med. 2023;48:471–7.
79. Sengupta S. Post-operative pulmonary complications after thoracotomy. Indian J Anaesth. 2015;59:618–26.
80. Visser E, Marsman M, van Rossum PSN, Cheong E, Al-Naimi K, van Klei WA, et al. Postoperative pain management after esophagectomy: a systematic review and meta-analysis. Dis Esophagus. 2017;30:1–11.
81. Odor PM, Bampoe S, Gilhooly D, Creagh-Brown B, Moonesinghe SR. Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. BMJ. 2020;368:m540.
82. Macrosson D, Beebeejaun A, Odor PM. A systematic review and meta-analysis of thoracic epidural analgesia versus other analgesic techniques in patients post-oesophagectomy. Perioper Med (Lond). 2024;13:80.
83. Weinstein EJ, Levene JL, Cohen MS, Andreae DA, Chao JY, Johnson M, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev. 2018;4:CD007105.
84. Balzani E, Rosboch GL, Ceraolo E, Lyberis P, Filippini C, Piccioni F, et al. The effect of peripheral regional analgesia in thoracic surgery: a systematic review and a meta-analysis of randomized-controlled trials. Tumori. 2023;109:6–18.
85. Yeung JHY, Gates S, Naidu BV, Wilson MJA, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev. 2016;2:CD009121.
86. Ding X, Jin S, Niu X, Ren H, Fu S, Li Q. A comparison of the analgesia efficacy and side effects of paravertebral compared with epidural blockade for thoracotomy: an updated meta-analysis. PLoS One. 2014;9:e96233.
87. Baidya DK, Khanna P, Maitra S. Analgesic efficacy and safety of thoracic paravertebral and epidural analgesia for thoracic surgery: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2014;18:626–35.
88. Xiong C, Han C, Zhao D, Peng W, Xu D, Lan Z. Postoperative analgesic effects of paravertebral block versus erector spinae plane block for thoracic and breast surgery: A meta-analysis. PLoS One. 2021;16:e0256611.
89. Koo C-H, Lee H-T, Na H-S, Ryu J-H, Shin H-J. Efficacy of erector spinae plane block for analgesia in thoracic surgery: A systematic review and meta-analysis. J Cardiothorac Vasc Anesth. 2022;36:1387–95.
90. Huang W, Wang W, Xie W, Chen Z, Liu Y. Erector spinae plane block for postoperative analgesia in breast and thoracic surgery: A systematic review and meta-analysis. J Clin Anesth. 2020;66:109900.
91. Guerra-Londono CE, Privorotskiy A, Cozowicz C, Hicklen RS, Memtsoudis SG, Mariano ER, et al. Assessment of intercostal nerve block analgesia for thoracic surgery: A systematic review and meta-analysis: A systematic review and meta-analysis. JAMA Netw Open. 2021;4:e2133394.
92. Lusianawati, Suhardi CJ, Sumartono C, Wungu CDK. Efficacy and safety of the serratus anterior block compared to thoracic epidural analgesia in surgery: Systematic review and meta-analysis. Tzu Chi Med J. 2023;35:329–37.
93. Liu X, Song T, Xu H-Y, Chen X, Yin P, Zhang J. The serratus anterior plane block for analgesia after thoracic surgery: A meta-analysis of randomized controlled trails. Medicine (Baltimore). 2020;99:e20286.
94. Jack JM, McLellan E, Versyck B, Englesakis MF, Chin KJ. The role of serratus anterior plane and pectoral nerves blocks in cardiac surgery, thoracic surgery and trauma: a qualitative systematic review. Anaesthesia. 2020;75:1372–85.
95. McLean SR, von Homeyer P, Cheng A, Hall ML, Mulligan MS, Cain K, et al. Assessing the benefits of preoperative thoracic epidural placement for lung

transplantation. J Cardiothorac Vasc Anesth. 2018;32:2654–61.
96. Garcia JP, Ashworth CL, Hage CA. ECMO in lung transplant: pre, intra and post-operative utilization—a narrative review. Curr Chall Thorac Surg. 2022;0:0–0.
97. Lenz N, Hirschburger M, Roehrig R, Menges T, Mueller M, Padberg W, et al. Application of continuous wound-infusion catheters in lung transplantation: A retrospective data analysis. Thorac Cardiovasc Surg. 2017;65:403–9.
98. Hutchins J, Apostolidou I, Shumway S, Kelly R, Wang Q, Foster C, et al. Paravertebral catheter use for postoperative pain control in patients after lung transplant surgery: A prospective observational study. J Cardiothorac Vasc Anesth. 2017;31:142–6.
99. Rigg JRA, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet. 2002;359:1276–82.
100. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis: A meta-analysis. JAMA. 2003;290:2455–63.
101. Carver A, Wou F, Pawa A. Do outcomes differ between thoracic epidurals and continuous fascial plane blocks in adults undergoing major abdominal surgery? Curr Anesthesiol Rep. 2023;14:25–41.
102. Bardia A, Sood A, Mahmood F, Orhurhu V, Mueller A, Montealegre-Gallegos M, et al. Combined epidural-general anesthesia vs general anesthesia alone for elective abdominal aortic aneurysm repair. JAMA Surg. 2016;151:1116–23.
103. Monaco F, Pieri M, Barucco G, Karpatri V, Redaelli MB, De Luca M, et al. Epidural analgesia in open thoraco-abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2019;57:360–7.
104. Guay J, Kopp S. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev. 2016;2017:CD005059.
105. Greco KJ, Brovman EY, Nguyen LL, Urman RD. The impact of epidural analgesia on perioperative morbidity or mortality after open abdominal aortic aneurysm repair. Ann Vasc Surg. 2020;66:44–53.
106. Hermanides J, Hollmann MW, Stevens MF, Lirk P. Failed epidural: causes and management. Br J Anaesth. 2012;109:144–54.
107. Holte K, Foss NB, Svensén C, Lund C, Madsen JL, Kehlet H. Epidural anesthesia, hypotension, and changes in intravascular volume. Anesthesiology. 2004;100:281–6.
108. Jackson CB, Desai J, Lee WA, Renfro LA. Utility of continuous paravertebral block after retroperitoneal abdominal aortic aneurysm repair. Ann Vasc Surg. 2024;104:124–31.
109. Minami K, Yoshitani K, Inatomi Y, Sugiyama Y, Iida H, Ohnishi Y. A retrospective examination of the efficacy of paravertebral block for patients requiring intraoperative high-dose unfractionated heparin administration during thoracoabdominal aortic aneurysm repair. J Cardiothorac Vasc Anesth. 2015;29:937–41.
110. Walker C, Carneiro J, Bersot CDA, Barros V, Aslanidis T. Unilateral erector spinae plane block as adjuvant for open repair of thoracoabdominal aortic aneurysm: Case report and literature review [Internet]. 2023. Available from: https://rgdoi.net/10.13140/RG.2.2.20265.98400
111. Elsharkawy H, El-Boghdadly K, Barrington M. Quadratus lumborum block: Anatomical concepts, mechanisms, and techniques. Anesthesiology. 2019;130:322–35.
112. Tran DQ, Bravo D, Leurcharusmee P, Neal JM. Transversus Abdominis Plane Block: A Narrative Review. Anesthesiology. 2019;131:1166-90.
113. Feltracco P, Carollo C, Barbieri S, Milevoj M, Pettenuzzo T, Gringeri E, et al. Pain control after liver transplantation surgery. Transplant Proc. 2014;46:2300–7.
114. Hausken J, Haugaa H, Hagness M, Line P-D, Melum E, Tønnessen TI. Thoracic epidural analgesia for postoperative pain management in liver transplantation: A 10-year study on 685 liver transplant recipients: A 10-year study on 685 liver transplant recipients. Transplant Direct. 2021;7:e648.
115. Dieu A, Huynen P, Lavand'homme P, Beloeil H, Freys SM, Pogatzki-Zahn EM, et al. Pain management after open liver resection: Procedure-Specific Postoperative Pain Management (PROSPECT) recommendations. Reg Anesth Pain Med. 2021;46:433–45.
116. Ander M, Mugve N, Crouch C, Kassel C, Fukazawa K, Isaak R, et al. Regional anesthesia for transplantation surgery - A White Paper Part 2: Abdominal transplantation surgery. Clin Transplant. 2024;38:e15227.
117. Guay J, Kopp S. Epidural analgesia for adults undergoing cardiac surgery with or without cardiopulmonary bypass. Cochrane Database Syst Rev. 2019;3:CD006715.
118. Ho AM, Chung DC, Joynt GM. Neuraxial blockade and hematoma in cardiac surgery: estimating the risk of a rare adverse event that has not (yet) occurred. Chest. 2000;117:551–5.
119. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American society of regional anesthesia and pain medicine evidence-based guidelines (fourth edition). Reg Anesth Pain Med. 2018;43:263–309.
120. Devarajan J, Balasubramanian S, Nazarnia S, Lin C, Subramaniam K. Regional Analgesia for Cardiac Surgery Part 1. Current status of neuraxial and paravertebral blocks for adult cardiac surgery. Semin Cardiothorac Vasc Anesth. 2021;25:252–64.
121. Naganuma M, Tokita T, Sato Y, Kasai T, Kudo Y, Suzuki N, et al. Efficacy of preoperative bilateral thoracic paravertebral block in cardiac surgery requiring full heparinization: A propensity-matched study. J Cardiothorac Vasc Anesth. 2022;36:477–82.
122. Scarfe AJ, Schuhmann-Hingel S, Duncan JK, Ma N, Atukorale YN, Cameron AL. Continuous paravertebral block for post-cardiothoracic surgery analgesia: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2016;50:1010–8.
123. Höhener D, Blumenthal S, Borgeat A. Sedation and regional anaesthesia in the adult patient. Br J Anaesth. 2008;100:8–16.
124. Elsharkawy H, Pawa A, Mariano ER. Interfascial plane blocks: Back to basics. Reg Anesth Pain Med. 2018;43:341–6.
125. Neal JM, Barrington MJ, Brull R, Hadzic A, Hebl JR, Horlocker TT, et al. The second ASRA practice advisory on neurologic complications associated with regional anesthesia and pain medicine: Executive summary 2015. Reg Anesth Pain Med. 2015;40:401–30.
126. Topor B, Oldman M, Nicholls B. Best practices for safety and quality in peripheral regional anaesthesia. BJA Educ. 2020;20:341–7.
127. Walker BJ, Long JB, Sathyamoorthy M, Birstler J, Wolf C, Bosenberg AT, et al. Complications in pediatric regional anesthesia: An analysis of more than 100,000 blocks from the Pediatric Regional Anesthesia Network: An analysis of more than 100,000 blocks from the pediatric regional anesthesia network. Anesthesiology. 2018;129:721–32.
128. Ramin S, Bringuier S, Martinez O, Sadek M, Manzanera J, Deras P, et al. Continuous peripheral nerve blocks for analgesia of ventilated critically ill patients with multiple trauma: a prospective randomized study. Anaesth Crit Care Pain Med. 2023;42:101183.

129. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the prevention and management of Pain, Agitation/sedation, Delirium, Immobility, and Sleep disruption in Adult Patients in the ICU. Crit Care Med. 2018;46:e825–73.
130. Vincent J-L, Sakr Y, Singer M, Martin-Loeches I, Machado FR, Marshall JC, et al. Prevalence and outcomes of infection among patients in intensive care units in 2017. JAMA. 2020;323:1478–87.
131. Selvamani BJ, Kalagara H, Volk T, Narouze S, Childs C, Patel A, et al. Infectious complications following regional anesthesia: a narrative review and contemporary estimates of risk. Reg Anesth Pain Med. 2024;rapm-2024-105496.
132. Rasouli MR, Cavanaugh PK, Restrepo C, Ceylan HH, Maltenfort MG, Viscusi ER, et al. Is neuraxial anesthesia safe in patients undergoing surgery for treatment of periprosthetic joint infection? Clin Orthop Relat Res. 2015;473:1472–7.
133. Neuburger M, Büttner J, Blumenthal S, Breitbarth J, Borgeat A. Inflammation and infection complications of 2285 perineural catheters: a prospective study. Acta Anaesthesiol Scand. 2007;51:108–14.
134. Capdevila X, Pirat P, Bringuier S, Gaertner E, Singelyn F, Bernard N, et al. Continuous peripheral nerve blocks in hospital wards after orthopedic surgery: a multicenter prospective analysis of the quality of postoperative analgesia and complications in 1,416 patients. Anesthesiology. 2005;103:1035–45.
135. Morin AM, Kerwat KM, Klotz M, Niestolik R, Ruf VE, Wulf H, et al. Risk factors for bacterial catheter colonization in regional anaesthesia. BMC Anesthesiol. 2005;5:1.
136. Bomberg H, Kubulus C, Herberger S, Wagenpfeil S, Kessler P, Steinfeldt T, et al. Tunnelling of thoracic epidural catheters is associated with fewer catheter-related infections: a retrospective registry analysis. Br J Anaesth. 2016;116:546–53.
137. Schmoch T, Möhnle P, Weigand MA, Briegel J, Bauer M, Bloos F, et al. The prevalence of sepsis-induced coagulopathy in patients with sepsis - a secondary analysis of two German multicenter randomized controlled trials. Ann Intensive Care. 2023;13:3.
138. Derakhshanfar H, Vafaei A, Tabatabaey A, Noori S. Prevalence and associated factors of acute traumatic coagulopathy; A cross sectional study. Emerg (Tehran). 2017;5:e58.
139. Kietaibl S, Ferrandis R, Godier A, Llau J, Lobo C, Macfarlane A Jr, et al. Regional anaesthesia in patients on antithrombotic drugs: Joint ESAIC/ESRA guidelines: Joint ESAIC/ESRA guidelines. Eur J Anaesthesiol. 2022;39:100–32.
140. Joubert F, Gillois P, Bouaziz H, Marret E, Iohom G, Albaladejo P. Bleeding complications following peripheral regional anaesthesia in patients treated with anticoagulants or antiplatelet agents: A systematic review. Anaesth Crit Care Pain Med. 2019;38:507–16.
141. Working Party:; Association of Anaesthetists of Great Britain & Ireland; Obstetric Anaesthetists' Association; Regional Anaesthesia UK. Regional anaesthesia and patients with abnormalities of coagulation: the Association of Anaesthetists of Great Britain & Ireland The Obstetric Anaesthetists' Association Regional Anaesthesia UK. Anaesthesia. 2013;68:966-72.
142. Arbona FL, Khabiri B, Norton JA. Ultrasound-Guided Regional Anesthesia: A Practical Approach to Peripheral Nerve Blocks and Perineural Catheters. Cambridge University Press; 2011. 207 p.
143. Dung-Hung C, Cong T, Zeyu J, Yu-Shan OY, Yung-Yan L. External validation of a machine learning model to predict hemodynamic instability in intensive care unit. Crit Care. 2022;26:215.
144. Meyhoff CS, Hesselbjerg L, Koscielniak-Nielsen Z, Rasmussen LS. Biphasic cardiac output changes during onset of spinal anaesthesia in elderly patients. Eur J Anaesthesiol. 2007;24:770-5.
145. Wink J, Veering BT, Aarts LPHJ, Wouters PF. Effects of thoracic epidural anesthesia on neuronal cardiac regulation and cardiac function. Anesthesiology. 2019;130:472–91.
146. Scott DA, Beilby DS, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. A prospective analysis of 1,014 patients. Anesthesiology. 1995;83:727-37.
147. Eichenberger U, Giani C, Petersen-Felix S, Graven-Nielsen T, Arendt-Nielsen L, Curatolo M. Lumbar epidural fentanyl: segmental spread and effect on temporal summation and muscle pain. Br J Anaesth. 2003;90:467-73.
148. Mohta M, Verma P, Saxena AK, Sethi AK, Tyagi A, Girotra G. Prospective, randomized comparison of continuous thoracic epidural and thoracic paravertebral infusion in patients with unilateral multiple fractured ribs–a pilot study. J Trauma. 2009;66:1096-101.
149. Frölich MA, Arabshahi A, Katholi C, Prasain J, Barnes S. Hemodynamic characteristics of midazolam, propofol, and dexmedetomidine in healthy volunteers. J Clin Anesth. 2011;23:218-23.
150. Tikle HA, Patil BM. Comparison of superficial cervical plexus block versus local infiltration for pain relief during internal jugular vein cannulation. Int J Contemp Med Res [IJCMR] [Internet]. 2018 Sep;5(9).
151. Lopez-Rincon RM, Kumar V. Ultrasound-guided intercostal nerve block. 2020; Available from: https://www.ncbi.nlm.nih.gov/books/NBK555900/

Turk J Intensive Care 2024;22:239-47
DOI: 10.4274/tybd.galenos.2023.82621

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Akif Demirel,
Ökkeş Hakan Miniksar

The Role of Inflammatory Indices in Predicting Intensive Care Unit Mortality in Critically Ill COVID-19 Patients

COVID-19 Kritik Hastalarında Yoğun Bakım Mortalitesini Öngörmede Enflamasyon İndekslerinin Rolü

Received/Geliş Tarihi : 23.06.2023
Accepted/Kabul Tarihi : 02.10.2023

Akif Demirel
Yozgat City Hospital, Clinic of Anesthesiology and Reanimation, Yozgat, Turkey

Ökkeş Hakan Miniksar
University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Anesthesiology and Reanimation, Ankara, Turkey

Akif Demirel DM, (✉),
Yozgat City Hospital, Clinic of Anesthesiology and Reanimation, Yozgat, Turkey

E-mail : akif_demirel19@hotmail.com
ORCID ID : orcid.org/0000-0002-3859-0742

ABSTRACT *Objective:* The estimation of disease severity based on early biomarkers may facilitate treatment and reduce mortality in patients with Coronavirus disease-2019 (COVID-19). The present retrospective, observational study evaluates the role of different inflammatory indices in predicting mortality in COVID-19 patients.
Materials and Methods: The prognostic value for the prediction of 30-day mortality of inflammatory parameters [C-reactive protein (CRP), ferritin, procalcitonin (PCT)] and neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, derived NLR, systemic inflammation index, CRP-to-lymphocyte ratio (CRP/L), CRP-to-albumin ratio, and neutrophil-to-lymphocyte and platelet ratio were evaluated upon the initial admission of 305 COVID-19 patients to the intensive care unit.
Results: In this study, APACHE score, ferritin, PCT and CRP/L were significantly higher in the non-survivors than in survivors. No significant differences were found in the other inflammatory indices. High ferritin (p: <0.001) and high APACHE scores (p: <0.001) were identified as predictors of in-hospital mortality in a ROC curve analysis. Only a high ferritin level was identified as an independent risk factor for mortality in a multivariate regression analysis (p=0.002).
Conclusion: Inflammatory indices were not identified as predictors of mortality in critically ill COVID-19 patients admitted to the intensive care unit in the present study; and only high ferritin levels among the parameters related to inflammation were identified as an independent risk factor for mortality.
Keywords: COVID-19, biomarker, inflammatory indices, ferritin, mortality

ÖZ *Amaç:* Kritik Koronavirüs hastalığı-2019 (COVID-2019) hastalarında hastalığın şiddetinin erken biyobelirteçler ile belirlenmesi tedaviyi kolaylaştırabilir ve mortaliteyi azaltabilir. Bu retrospektif gözlemsel çalışmada, farklı enflamatuvar indekslerin COVID-19 hastalarında mortaliteyi tahmin etmedeki rollerini belirlemek amaçlandı.
Gereç ve Yöntem: İnflamatuar parametrelerin [C-reaktif protein (CRP), ferritin, prokalsitonin (PCT)] ve nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı, türetilmiş NLR, sistemik inflamasyon indeksi, CRP-lenfosit oranı (CRP/L), CRP-albümin oranı ve nötrofil-lenfosit-trombosit oranı gibi parametrelerin 30 günlük mortaliteyi öngörmedeki prognostik değerleri, yoğun bakım ünitesine kabul edilen 305 COVID-19 hastasında değerlendirildi.
Bulgular: Bu çalışmada, APACHE skoru, ferritin, PCT ve CRP/L değerleri, hayatta kalamayan hastalarda hayatta kalanlara kıyasla anlamlı derecede daha yüksekti. Diğer inflamatuar indekslerde anlamlı bir fark bulunmadı. ROC eğrisi analizinde, yüksek ferritin düzeyleri (p < 0.001) ve yüksek APACHE skorları (p < 0.001), hastane içi mortalitenin öngörücüleri olarak tanımlandı. Çok değişkenli regresyon analizinde ise yalnızca yüksek ferritin seviyesi mortalite için bağımsız bir risk faktörü olarak belirlendi (p = 0.002).
Sonuç: Yoğun bakımda yatan kritik COVID-19 hastalarında mortaliteyi öngörmede, çalışmamızda incelediğimiz enflamasyon indekslerinin prediktör olmadıkları, enflamasyon ile ilgili olarak sadece yüksek ferritin düzeylerinin mortalite için bağımsız risk faktörü olduğu saptandı.
Anahtar Kelimeler: COVID-19, biyobelirteç, enflamatuvar indeksler, ferritin, mortalite

Introduction

The first case of Coronavirus disease-2019 (COVID-19) was reported in the city of Wuhan (Hubei, China), which walter named COVID-19 by the World Health Organization. It is a contagious disease that continues to threatenglobal public health. The causative agent is referred to as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) because of its similarity with SARS-CoV (1).

COVID-19 manifests with mild symptoms in most patients, although a considerable number of patients suffer from severe rapidly progressing pneumonia leading to multi-organ failure, acute respiratory distress syndrome (ARDS), septic shock, and death (2). It is important to identify prognostic factors for reducing COVID-19-related mortality in high-risk patients who are followed up in the intensive care unit (ICU). There remains a need for clinical studies on this subject (3-5).

Accumulating evidence in the literature suggests that an increased inflammatory response is responsible for fatal complications in critically ill patients with COVID-19 (3). Hyperinflammation plays an important role in viral pathogenesis. Microvascular endothelial dysfunction occurs as a result of hyperinflammatory response and severe cytokine stormleadsto multi-organ failure and death in patients (6). Significant increases in the levels of serum ferritin, procalcitonin, C-reactive protein (CRP), interleukin-6, and other acute phase reactants are associated with mortality and prognosis in patients with COVID-19 (6).

The peripheral white blood cell count (WBC) and differential WBC counts (neutrophil, lymphocyte, platelet, monocyte) obtained by complete blood count (CBC) can be considered good biomarkers of systemic inflammatory response in critically ill patients. In recent studies in the literature, various inflammatory indices [i.e., neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio LMR), platelet-lymphocyte ratio (PLR), derived NLR (dNLR), systemic inflammation index (SII), aggregate Index of systemic inflammation (AISI), systemic inflammation response index (SIRI) and CPR/lymphocyte ratio (CRP/L)] have been investigated for their use as predictors of poor prognosis in patients with COVID-19, although these studies have yielded inconsistent results regarding the relationship between these biomarkers and prognosis (7). It is hypothesized in the present study that all these indices could serve as independent predictors of prognosis in patients with COVID-19. Thus, the present study evaluated the value of inflammatory indices and parameters for predicting prognosis in critically ill patients with COVID-19.

Materials and Methods

Ethical Statement

The study was conducted in the tertiary ICU of Yozgat City Hospital between May 2020 and May 2021. The study was approved by the Ethics Committee of Yozgat Bozok University (protocol number: 2017-KAEK-189_2021.09.27_03) and was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design

For this single-center retrospective study, clinical, demographic, and laboratory data were retrieved from the hospital's information management system and patient charts.

The study included adult ICU patients aged 18 years and older with a positive polymerase chain reaction test for COVID-19. After reviewing the patients' records, we excluded those with hematological disorders, those with a history of severe liver disease and malignancy, those younger than 18 years of age, and those with missing laboratory data were excluded from the study.

Study Participants

The age, sex, acute physiology and chronic health evaluation (APACHE 2) score, comorbidities, length of ICU stay, 30-day ICU mortality, need for mechanical ventilation in the first 24 hours, and need for inotropic support and renal placement therapy while in the ICU were recorded. Patients requiring mechanical ventilator support were defined as those undergoing resuscitation and endotracheal intubation due to cardiac or respiratory arrest. Patients were evaluated in two groups: Survivors (dischargedto home or transfer to the ward) and non-survivors (death during the ICU stay). The laboratory parameters measured upon admission to the ICU, including CRP, procalcitonin, ferritin, WBC, differential neutrophil, platelet, and lymphocyte counts, and mean platelet volume, were retrieved from the hospital's information management system.

Laboratory Measurements

The laboratory parameters measured in each patient from the venous blood samples collected upon admission to the ICU were retrieved from the hospital's information

management system. Inflammatory indices were calculated using CBC parameters as follows:

- SII= (neutrophil count×platelet count)/lymphocyte count;
- dNLR= neutrophil count/(WBC-neutrophil count);
- NLPR= (neutrophil count/lymphocyte count)×platelet count;
- CRP/albumin ratio= CRP/albumin, CRP/L=CRP/lymphocyte count;
- PLR= platelet/lymphocyte.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics Standard Concurrent User V 25 (IBM Corp., Armonk, NY USA). Categorical data are presented in n and frequency, whereas continuous data were presented in mean ± standard deviation and median [interquartile range (IQR): 25th-75th percentile]. The normality of distribution was checked using the Kolmogorov-Smirnov test and histograms. The significance of differences between groups in terms of averages was assessed using the chi-square test, independent samples t-test, and Mann-Whitney U test. In cross tables, Fisher's exact test was performed if more than 20% of the expected values were less than 5 or at least one of the values was less than 2. All significant variables were included in the multivariate logistic analysis after the univariate analysis. The factors predicting the mortality of patients with COVID-19 were investigated using a backward stepwise multivariate logistic regression analysis. The Hosmer-Lemeshow test for goodness-of-fit statistics was used to determine the calibration validation and discrimination of this regression analysis. The receiver operating characteristic (ROC) curve analysis was used to determine the parameters that had the greatest predictive value for the mortality of patients with COVID-19, and the areas under the curve (AUC) were calculated.

Results

Demographic and Clinical Characteristics

A total of 305 patients with COVID-19 (184 male; 121 female) were included in the study (Table 1). The median age was 72 years (IQR: 65-80 years). Of the total, 88 patients

Table 1. Comparison of demographic and clinical characteristics of survivors and non-survivors

Variables	Overall (n=305)	Non-survivors (n=217)	Survivors (n=88)	p-value
Age (years)	72 [65 to 80]	73 [66 to 81]	71.5 [59.5 to 79]	0.560
APACHE score	23 [17 to 35]	27 [18 to 37]	19 [14 to 27]	**0.000**
Length of ICU stay (days)	9 [4 to 15]	10 [5 to 17]	7.5 [4 to 10]	**0.002**
Sex, female/male	121/184 (39.7/60.3)	79/138 (36.4/63.6)	42/46 (47.7/52.3)	0.067#
Comorbidities, n (%)				
Hypertension	147 (48.2)	106 (48.8)	41 (46.6)	0.721#
CHF	39 (12.8)	26 (12.0)	13 (14.8)	0.647*
Diabetes mellitus	55 (18.0)	40 (18.4)	15 (17.0)	0.903*
Neurologic disease	54 (17.7)	40 (18.4)	14 (15.9)	0.721*
Arrhythmia	20 (6.6)	15 (6.9)	5 (5.7)	0.890*
CAD	78 (25.6)	57 (26.3)	21 (23.9)	0.771*
CKD	72 (23.6)	62 (28.6)	10 (11.4)	**0.002***
COPD	96 (31.5)	60 (27.6)	36 (40.9)	**0.024#**
Other	75 (24.7)	57 (26.4)	18 (20.5)	0.346*
Need for MV in the first 24 hours	244 (80.0)	195 (89.9)	49 (55.7)	**<0.001***
Need for vasoactive agent	45 (14.8)	42 (19.4)	3 (3.4)	**0.001***
Renal replacement therapy	102 (33.6)	83 (38.2)	19 (21.8)	**0.006#**

Data are presented as medians [interquartile range] for continuous variables and as numbers and percentages for categorical variables. Continuous variables were compared with a Mann-Whitney U test. Compared by the #: chi-square test and Yates's correction for continuity. The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold.
APACHE: Acute physiology and chronic health evaluation, ICU: intensive care unit, CHF: chronic heart failure, CAD: coronary artery disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, MV: mechanical ventilation

(28.9%) were discharged (survivors), and the remaining 217 patients (71.1%) died (non-survivors). Comorbidities included hypertension (48.2%), chronic obstructive pulmonary disease (31.5%), and coronary artery disease (25.6%). The median length of ICU stay was 9 days (IQR: 4-15 days).

As shown in Table 1, the APACHE score (27, IQR: 18-37 vs. 19, IQR: 14-27; p<0.001) was significantly higher, and the length of ICU stay was longer (median: 10.0 days, IQR: 5-17 days vs. 7.5 days, IQR: 4-10 days; p=0.002), chronic kidney disease (79% vs. 51%, p=0.002) was more common, and chronic obstructive pulmonary disease was less common (27.6% vs. 40.9%, p=0.024) in the non-survivors than in the survivors. The need for mechanical ventilation in the first 24 hours (89.9% vs. 57.7%, p<0.001), the need for vasoactive agents (19.4% vs. 3.4%, p=0.001), and the need for renal replacement therapy (38.2% vs. 21.8%, p=0.006) were higher in the non-survivors than in the survivors.

Laboratory Parameters and Inflammatory Indices

An analysis of the laboratory parameters revealed (Table 2) significantly higher ferritin (median: 458; IQR: 237-787 vs. 257, IQR: 125.5-506; p<0.001) and PCT (median: 0.44; IQR: 0.13-1.68 vs. 0.175 IQR: 0.09-0.52, p<0.001) values among the inflammatory parameters; significantly higher urea (median: 63; IQR: 44-106 vs. 52 IQR: 33.5-80, p=0.003) and creatinine (median: 1.17; IQR: 0.87-1.83 vs. 0.99 IQR: 0.76-1.21, p=0.001) values among the biochemical parameters; and significantly higher CRP/L (median: 19.75; IQR: 8.30-44.50 vs. 13.3 IQR: 3.7-30.2, p=0.028) values

Table 2. Comparison of laboratory variables between survivors and non-survivors

Variables	Overall (n=305)	Non-survivors (n=217)	Survivors (n=88)	p-value
Inflammatory parameters				
CRP (mg/dL)	11.2 [7.01 to 21.5]	11.6 [7.29 to 22.7]	10.2 [3.95 to 18.9]	0.053
Ferritin (ng/dL)	413 [182 to 709]	458 [237 to 787]	257 [125.5 to 506]	**<0.001**
PCT (ng/mL)	0.35 [0.12 to 1.21]	0.44 [0.13 to 1.68]	0.175 [0.09 to 0.52]	**<0.001**
Biochemical parameters				
Urea (mg/dL)	60 [42 to 93]	63 [44 to 106]	52 [33.5 to 80]	**0.003**
Creatinine (mg/dL)	1.09 [0.83 to 1.59]	1.17 [0.87 to 1.83]	0.99 [0.76 to 1.21]	**0.001**
Albumin (g/dL)	3.19 (0.48)	3.17 (0.44)	3.24 (0.56)	0.293†
Complete blood count				
WBC ($\times 10^9$ L)	8.6 [6.1 to 12.9]	8.4 [6.2 to 12.7]	9.05 [6.1 to 13.3]	0.850
Neutrophils ($\times 10^9$ L)	7.5 [4.7 to 11.6]	7.4 [4.8 to 11.3]	7.8 [4.3 to 11.9]	0.925
Lymphocytes ($\times 10^9$ L)	0.7 [0.4 to 1]	0.7 [0.4 to 1]	0.8 [0.45 to 1.1]	0.076
Platelets ($\times 10^9$ L)	202 [154 to 271]	200 [149 to 259]	209 [165 to 281.5]	0.134
MPV (fL)	8.4 [7.8 to 9.1]	8.4 [7.9 to 9.1]	8.4 [7.75 to 9.1]	0.922
Inflammatory indices				
SII	2079.75 [938 to 4566]	2120 [1001 to 4442]	2063 [899 to 4942]	0.879
NLR	10.8 [5.5 to 19.3]	10.8 [5.8 to 19.2]	9.56 [4.54 to 21.25]	0.328
dNLR	5.66 [3.35 to 10.33]	5.66 [3.4 to 10.42]	5.02 [2.84 to 10.1]	0.222
NLPR	5.08 [2.90 to 10.40]	5.16 [3.13 to 10.58]	4.71 [2.46 to 9.22]	0.139
CRP/alb	3.55 [2.03 to 7.08]	3.8 [2.2 to 7.5]	3.17 [1.12 to 6.22]	0.058
CRP/L	16.66 [6.95 to 41]	19.75 [8.30 to 44.66]	13.3 [3.7 to 30.2]	**0.028**
PLR	290 [174 to 503]	300 [180 to 498]	253.35 [163 to 540]	0.693

Values are quoted as mean (standard deviation) and median [interquartile range]. †: Compared by independent sample t-test. Other values were compared with a Mann-Whitney U test. The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold.
CRP: C-reactive protein, PCT: procalcitonin, WBC: white blood cell, MPV: mean platelet volume, SII: systemic immune-inflammation index, NLR: neutrophil-to-lymphocyte ratio, dNLR: derived neutrophil-to-lymphocyte ratio, NLPR: neutrophil-to-lymphocyte, platelet ratio, CRP/alb: C-reactive protein-to-albumin ratio, CRP/L: C-reactive protein-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio

among the inflammatory indices in the non-survivors than in the survivors. On the other hand, there were no significant differences in the CRP, albumin, and CBC parameters and other (SII, NLR, dNLR, NLPR, CRP/Alb, CRP/L, PRL,) inflammatory indices between the survivors and non-survivors (Table 2).

Predictive Accuracy of Laboratory Parameters for Mortality

In the ROC curve analysis for mortality in patients with COVID-19, the optimal cut-off value was 19.5 [AUC=0.672, 95% confidence interval (CI) 0.607-0.736, p<0.001] for the APACHE score and 263.0 ng/dL (AUC=0.627, 95% CI 0.559-0.696, p<0.001) for ferritin (Table 3). Among the other inflammatory parameters, the ROC curve analysis for CRP/L did not reveal a significant level for the prediction of mortality in patients with COVID-19 (p<0.05).

Risk Factors for COVID-19 Mortality in Univariate and Multivariate Analyses

The ICU mortality rate in the entire study population was 71.1%. The results of univariate and multivariate logistic regression analyses for mortality among patients with COVID-19 are presented in Table 4.

In the univariate analysis, the APACHE score, ferritin, urea, and creatinine were identified as significant predictors of mortality, whereasin the multivariate analysis, high ferritin levels [odds ratio (OR)=0.999; 95% CI 0.998-1.000; p=0.002] and APACHE score (OR=0.947; 95% CI 0.923-0.972; p<0.001) were identified as independent predictors of mortality (Figure 1).

Discussion

The present study evaluating the relationship between inflammatory indices, based on the laboratory parameters measured upon initial admission, and mortality in critically ill COVID-19 patients has produced several important results. Ferritin, urea, and creatinine levels were higher in the non-survivors than in the survivors. Among the inflammatory indices, CRP/L was higher in the non-survivors. High ferritin levels and APACHE scores were independent predictors of mortality.

Predicting prognosis is of utmost importance in critically ill patients with COVID-19 who have a high mortality rate. Clinical studies have generally reported decreased T lymphocyte and CD3, CD4, and CD8 levels together with an

Table 3. ROC curve analysis predicting the mortality of COVID-19 patients

Variables	AUC	Cut-off point	Sensitivity (%)	Specificity (%)	p-value	95% CI	
						Lower	Upper
APACHE score	0.672	19.5	70.0	51.1	**<0.001**	0.607	0.736
Ferritin	0.627	263.0	71.0	50.0	**<0.001**	0.559	0.696

The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold.
AUC: Area under the curve, APACHE: acute physiology and chronic health evaluation, CI: confidence interval, COVID-19: coronavirus disease-2019, ROC: receiver operating characteristic

Table 4. Univariate and multivariate analysis for the mortality of COVID-19 patients

Variables	Univariate analysis			Multivariate analysis		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
APACHE score	0.944	(0.921-0.964)	**<0.001**	0.947	(0.923-0.972)	**<0.001**
CRP	0.978	(0.955-1.001)	0.066			
Ferritin	0.999	(0.998-1.000)	**0.002**	0.999	(0.998-1.000)	**0.002**
PCT	0.963	(0.917-1.012)	0.140			
Urea	0.992	(0.986-0.998)	**0.007**	0.996	(0.990-1.002)	0.196
Creatinine	0.671	(0.499-0.903)	**0.008**			
CRP/L	0.993	(0.985-1.001)	0.098			

Multivariate Model's Adjusted R^2=0.183, p-value <0.001.
The level of statistical significance was set at 0.05. All statistically significant values are indicated in bold.
APACHE: Acute physiology and chronic health evaluation, CRP: C-reactive protein, CRP/L: CRP-to-lymphocyte ratio, CI: confidence interval, PCT: procalcitonin, OR: odds ratio, COVID-19: coronavirus disease-2019

increase in proinflammatory cytokines. Cytokine storms have been linked to disease severity, leading to multi-organ failure and death (8). In such cases, the increase in the number of inflammatory cells at the level of the endothelium is known to impair microcirculation and to cause systemic impairment in different organs in COVID-19 patients (6). Further studies have reported various laboratory abnormalities in response to an exaggerated inflammatory response in critically ill patients with COVID-19 (9,10), and these resultsresults are important indicators of systemic inflammation and immune response (9,11). Many studies have evaluated the relationship between inflammatory biomarkers and poor outcomes in patients with COVID-19 (10-13). The present study aimed to analyze the predictive value of inflammatory indices derived from inflammatory markers on mortality in critically ill patients with COVID-19 who exhibit an exaggerated immune response.

Before the COVID-19 pandemic, a significant increase in CRP concentrations was most frequently attributed to a condition caused by a bacterial pathogen (14). However, elevated CRP levels have also been reported in severe viral infections, including pneumonia caused by H1N1 influenza, and particularly in COVID-19 patients in recent years (15,16). Furthermore, as a biomarker of inflammation, CRP is strongly linked to disease severity, ARDS, and mortality in such patients (17). Yang et al. (18) reported CRP/L as a

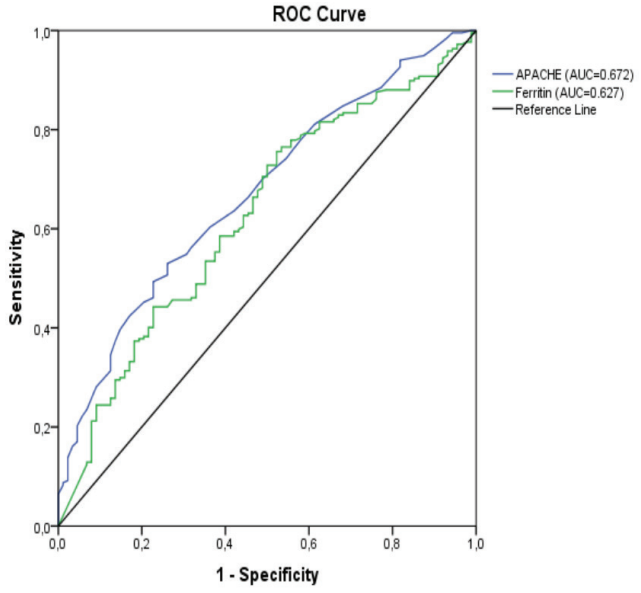

Figure 1. ROC curve

ROC: Receiver operating characteristic, APACHE: Acute physiology and chronic health evaluation, AUC: Area under the curve

highly sensitive indicator of disease severity in patients with early COVID-19 pneumonia, and while similar to the present study, they reported a higher CRP/L ratio in non-survivors, CRP/L did not predict mortality in a univariate regression analysis. In contrast to the findings of the present study, Ullah et al. (19) reported the lymphocyte-to-CRP ratio (LCR) to be a sensitive predictor of the inflammatory cascade and should be considered as a potential new predictor of in-hospital mortality and poor outcomes in patients with COVID-19. The same study reported an association between an increased risk of in-hospital mortality and low LCR (19). In another study, Acar et al. (20) reported that LCR was a significant independent predictor of in-hospital mortality in 148 patients. LCR has high sensitivity in the acute phase of inflammation because CRP levels increase early before the emergence of neutrophilia or lymphopenia, regardless of the reasons for the elevated levels (i.e., infections, cancer, autoimmune) (19). For this reason, elevated LCR may be regarded as an independent biomarker of the initial stages of inflammation. Although it is well established that the NLR correlates with the severity of COVID-19, it is important to know that the NLR can be affected in immunosuppressed patients or in those receiving high-dose corticosteroid therapy (21). For this reason, the authors believe the low CLR is attributable to the fact that all patients were initiated on corticosteroid therapy upon admission to the ICU.

Ferritin, an inflammatory parameter, plays an important role in mortality in patients with COVID-19. Lucijanic et al. (22) reported that elevated ferritin levels were associated with poorer prognosis and death in patients with COVID-19 than in those with low ferritin levels. In their study, Hou et al. (23) suggested the use of ferritin as a predictor of disease severity in critically ill COVID-19 patients based on their multivariate logistic regression analysis (23), whereas Cecconi et al. (24) reported that ferritin could be useful for the early identification of a risk of deterioration in the clinical condition of hospitalized COVID-19 patients that may result in transfer to the ICU or death, and in the determination of the treatment approach. Elevated ferritin levels, a marker of inflammation, have been associated with increased mortality considering their contribution to the development of both cytokine storms and ARDS (25). Consistent with these studies, the multivariate logistic regression analysis in the present study found that only elevated ferritin levels could serve as an independent indicator of mortality.

Under normal circumstances, procalcitonin is produced and released into circulation by the parafollicular C-cells in the thyroid gland, and is produced in substantial quantities in extrathyroidal tissues during severe infections (26) and maintained by increased interleukin (IL)-1β, tumor necrosis factor-α and IL-6 concentrations. Procalcitonin has been reported to better differentiate between bacterial infections and other inflammatory processes than WBC count and CRP (27). Although Lippi and Plebani (28) found that bacterial co-infection resulted in elevated procalcitonin levels, Kotula et al. (29) reported elevated procalcitonin levels in patients with confirmed viral infection but without bacterial infection. In another study, higher procalcitonin levels were identified in critically ill COVID-19 patients than in those without critical illness (30). Similarly, procalcitonin levels were significantly higher in non-survivors than in survivors. In a meta-analysis of four studies, Lippi and Plebani (28) reported that serial procalcitonin measurement was useful for predicting prognosis in patients with COVID-19. The authors of the present study believe that although COVID-19 is a viral infection, platelet-to-lymphocyte ratio (PTC) measurement could be useful in predicting prognosis and could support treatment decisions in patients with COVID-19.

There are several studies in the literature investigating the relationship between various inflammatory indices and prognosis and mortality in COVID-19. Ding et al. (31) reported a significant relationship between NLR after the fifth day of hospital admission and the length of hospital stay in 72 patients with COVID-19 and suggested that NLR measured after the fifth day of hospitalization could be used to predict prognosis in hospitalized patients with COVID-19. Seyit et al. (32) reported that PRL upon initial admission to the emergency room showed a better correlation with disease severity than NLR in 110 COVID-19 patients (32). When the findings of the present study are examined in detail, inflammatory indices, such as NLR, PLR, dNLR, SII, CRP/alb, and NPLR, which are known to predict prognosis in patients with COVID-19, were found to be unrelated to mortality.

In a study of 114 patients with COVID-19, Xue et al. (33) reported that NLR, PLR, dNLR, and SII, measured at the time of admission to the hospital, were insufficient for predicting disease severity, although they did not evaluate mortality rates. Similarly, in a study evaluating the SII measured from blood tests performed within 1 hour of hospitalization in 285 patients, Kudlinski et al. (34) identified no significant value of the SII in predicting mortality.

In addition, Ullah et al. (19) compared LCR and NLR in terms of their performance in predicting in-hospital mortality in the early period and found that NLR could significantly predict mortality and the need for mechanical ventilation on day 7, whereas NLR measured on day 1 had no significant predictive power. They also reported that the values may vary, with the potential to be increased in those receiving steroid therapy and decreased in those with bone marrow suppression due to cancer or chemotherapy (19). The authors of the present study believe that the inflammatory indices of the study patients may have been affected considering that all critically ill patients requiring oxygen supplementation due to respiratory distress, unless contraindicated, received dexamethasone 6 mg/day, prednisolone 0.5-1 mg/kg, or its equivalent methylprednisolone for 10 days, as per the treatment guidelines published by the Ministry of Health of Turkey (35).

Study Limitations

The present study has some limitations, the first of which is its retrospective and single-center design. Multicenter studies will certainly contribute significantly to the literature. The second limitation is that the administration of steroid therapy to patients without contraindications, as per the treatment protocols, may have affected the inflammatory indices, although the studied inflammatory markers were comparable considering that these therapies have been standardized. The strengths of the present study include its sample of 305 ICU patients, and the ICU follow-up and treatment of these patients had been performed by the same team. An additional strength of the study to be considered is its simultaneous examination of multiple parameters in the same patient group, which have been evaluated in dispersed groups in previous studies.

Conclusion

In the present study, inflammatory indices were not identified as predictors of mortality in critically ill patients with COVID-19 admitted to the ICU, and only high ferritin levels were identified as independent risk factors for mortality. Ferritin levels at the time of admission to the ICU can be useful for predicting prognosis in critically ill ICU patients, including those with COVID-19.

Ethics

Ethics Committee Approval: The study was conducted in the tertiary ICU of Yozgat City Hospital between May 2020 and May 2021. The study was approved by the Ethics Committee of Yozgat Bozok University (protocol number: 2017-KAEK-189_2021.09.27_03) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.D., Concept: Ö.K.M., Design: A.D., Data Collection or Processing: A.D., Analysis or Interpretation: Ö.K.M., Literature Search: A.D., Writing: A.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323:1574-81.
2. van Eijk LE, Binkhorst M, Bourgonje AR, Offringa AK, Mulder DJ, Bos EM, et al. COVID-19: immunopathology, pathophysiological mechanisms, and treatment options. J Pathol. 2021;254:307-31.
3. Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504.
4. Doganci S, Ince ME, Ors N, Yildirim AK, Sir E, Karabacak K, et al. A new COVID-19 prediction scoring model for in-hospital mortality: experiences from Turkey, single center retrospective cohort analysis. Eur Rev Med Pharmacol Sci. 2020;24:10247-57.
5. Usul E, Şan İ, Bekgöz B, Şahin A. Role of hematological parameters in COVID-19 patients in the emergency room. Biomark Med. 2020;14:1207-15.
6. 6.Tomar B, Anders HJ, Desai J, Mulay SR. Neutrophils and Neutrophil Extracellular Traps Drive Necroinflammation in COVID-19. Cells. 2020;9:1383.
7. Karimi A, Shobeiri P, Kulasinghe A, Rezaei N. Novel Systemic Inflammation Markers to Predict COVID-19 Prognosis. Front Immunol. 2021;12:741061.
8. Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. Molecules. 2020;25:5725.
9. Rokni M, Ahmadikia K, Asghari S, Mashaei S, Hassanali F. Comparison of clinical, para-clinical and laboratory findings in survived and deceased patients with COVID-19: diagnostic role of inflammatory indications in determining the severity of illness. BMC Infect Dis. 2020;20:869.
10. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting Disease Severity and Outcome in COVID-19 Patients: A Review of Multiple Biomarkers. Arch Pathol Lab Med. 2020;144:1465-74.
11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
12. Paliogiannis P, Zinellu A, Scano V, Mulas G, De Riu G, Pascale RM, et al. Laboratory test alterations in patients with COVID-19 and non COVID-19 interstitial pneumonia: a preliminary report. J Infect Dev Ctries. 2020;14:685-90.
13. Gerotziafas GT, Sergentanis TN, Voiriot G, Lassel L, Papageorgiou C, Elabbadi A, et al. Derivation and Validation of a Predictive Score for Disease Worsening in Patients with COVID-19. Thromb Haemost. 2020;120:1680-90.
14. Vanderschueren S, Deeren D, Knockaert DC, Bobbaers H, Bossuyt X, Peetermans W. Extremely elevated C-reactive protein. Eur J Intern Med. 2006;17:430-3.
15. Vasileva D, Badawi A. C-reactive protein as a biomarker of severe H1N1 influenza. Inflamm Res. 2019;68:39-46.
16. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic Value of C-Reactive Protein in Patients With Coronavirus 2019. Clin Infect Dis. 2020;71:2174-9.
17. Smilowitz NR, Kunichoff D, Garshick M, Shah B, Pillinger M, Hochman JS, et al. C-reactive protein and clinical outcomes in patients with COVID-19. Eur Heart J. 2021;42:2270-9.
18. Yang M, Chen X, Xu Y. A Retrospective Study of the C-Reactive Protein to Lymphocyte Ratio and Disease Severity in 108 Patients with Early COVID-19 Pneumonia from January to March 2020 in Wuhan, China. Med Sci Monit. 2020;26:e926393.
19. Ullah W, Basyal B, Tariq S, Almas T, Saeed R, Roomi S, et al. Lymphocyte-to-C-Reactive Protein Ratio: A Novel Predictor of Adverse Outcomes in COVID-19. J Clin Med Res. 2020;12:415-22.
20. Acar E, Demir A, Yıldırım B, Kaya MG, Gökçek K. The role of hemogram parameters and C-reactive protein in predicting mortality in COVID-19 infection. Int J Clin Pract. 2021;75:e14256.
21. Tonduangu N, Le Borgne P, Lefebvre F, Alame K, Bérard L, Gottwalles Y, et al. Prognostic Value of C-Reactive Protein to Lymphocyte Ratio (CLR) in Emergency Department Patients with SARS-CoV-2 Infection. J Pers Med. 2021;11:1274.
22. Lucijanic M, Demaria M, Gnjidic J, Rob Z, Filipovic D, Penovic T, Jordan A, Barisic-Jaman M, Pastrović F, Lucijanic D, Cikara T, Lucijanic T, Miletic M, Ljubicic D, Keres T. Higher ferritin levels in COVID-19 patients are associated with hyperinflammation, worse prognosis, and more bacterial infections without pronounced features of hemophagocytosis. Ann Hematol. 2022 May;101(5):1119-1121. doi: 10.1007/s00277-022-04813-y. Epub 2022 Mar 11. PMID: 35275231; PMCID: PMC8916070.
23. Hou H, Zhang B, Huang H, Luo Y, Wu S, Tang G, et al. Using IL-2R/lymphocytes for predicting the clinical progression of patients with COVID-19. Clin Exp Immunol. 2020;201:76-84.
24. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, et al. Early Predictors of Clinical Deterioration

in a Cohort of 239 Patients Hospitalized for Covid-19 Infection in Lombardy, Italy. J Clin Med. 2020;9:1548.
25. Para O, Caruso L, Pestelli G, Tangianu F, Carrara D, Maddaluni L, et al. Ferritin as prognostic marker in COVID-19: the FerVid study. Postgrad Med. 2022;134:58-63.
26. Cleland DA, Eranki AP Procalcitonin. StatPearls; [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. [cited: 2020 Apr 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK539794/
27. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57:389-99.
28. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020;505:190-1.
29. Kotula JJ, Moore WS, Chopra A, Cies JJ. Association of Procalcitonin Value and Bacterial Coinfections in Pediatric Patients With Viral Lower Respiratory Tract Infections Admitted to the Pediatric Intensive Care Unit. J Pediatr Pharmacol Ther. 2018;23:466-72.
30. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730-41.
31. Ding X, Yu Y, Lu B, Huo J, Chen M, Kang Y. Dynamic profile and clinical implications of hematological parameters in hospitalized patients with coronavirus disease 2019. Clin Chem Lab Med. 2020;58:1365-71.
32. Seyit M, Avci E, Nar R, Senol H, Yilmaz A, Ozen M, et al. Neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio to predict the severity of COVID-19. Am J Emerg Med. 2021;40:110-4.
33. Xue G, Gan X, Wu Z, Xie D, Xiong Y, Hua L, et al. Novel serological biomarkers for inflammation in predicting disease severity in patients with COVID-19. Int Immunopharmacol. 2020;89:107065.
34. Kudlinski B, Zgoła D, Stolińska M, Murkos M, Kania J, Nowak P, et al. Systemic Inflammatory Predictors of In-Hospital Mortality in COVID-19 Patients: A Retrospective Study. Diagnostics. 2022;12:859.
35. COVID-19 Rehberi [İnternet]. T.C. Sağlık Bakanlığı COVID-19 Bilgilendirme Platformu. [erişim tarihi: 7 Kasım 2020]. Erişim adresi: https://covid19.saglik.gov.tr/TR-66341/antisitokin-antiinflamatuar-tedaviler-koagulopati-yonetimi.html

Turk J Intensive Care 2024;22:248-55
DOI: 10.4274/tybd.galenos.2023.60362

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Kadir Arslan,
Ayça Sultan Şahin

Evaluation of Early and Late Tracheostomy Applications in Intensive Care Patients Before and After the COVID-19 Pandemic: Four-year Tertiary Center Experience

COVID-19 Pandemisi Öncesi ve Sonrasında Yoğun Bakım Hastalarında Gerçekleştirilen Erken ve Geç Trakeostomi Uygulamalarının Değerlendirilmesi: Dört Yıllık Tersiyer Merkez Deneyimi

Received/Geliş Tarihi : 01.10.2022
Accepted/Kabul Tarihi : 12.10.2023

Kadir Arslan, Ayça Sultan Şahin
University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Department of Anesthesiology and Reanimation, İstanbul, Turkey

Kadir Arslan MD, (✉),
University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Department of Anesthesiology and Reanimation, İstanbul, Turkey

E-mail : kadir.arslan@sbu.edu.tr
ORCID ID : orcid.org/0000-0003-4061-0746

ABSTRACT *Objective:* The Coronavirus disease-2019 (COVID-19) pandemic has resulted in a critical need for optimal tracheostomy time. This study investigated the effects of early and late tracheostomy procedures performed in a tertiary center's intensive care unit (ICU) on patient outcomes and mortality during the four years before and after the COVID-19 pandemic.
Materials and Methods: This retrospective cross-sectional study included patients who underwent percutaneous tracheostomy in the ICU between March 2018 and March 2022. Patients were classified into Group 1 (early <10 days) and Group 2 (late ≥10 days) and evaluated before and after the COVID-19 pandemic. Demographic data, clinical features, and mortality were analyzed.
Results: A total of 137 patients were included in the study. Among the study population, 62% were male, and 29.1% underwent early tracheostomy. Although the mean age of patients in Group 1 and the length of stay in the ICU were significantly lower, no significant difference was found between the groups in terms of mortality. Cranial pathologies were the most common indication for ICU hospitalization among patients who underwent tracheostomy before the pandemic, whereas COVID-19 was observed during the pandemic period. The COVID-19 pandemic had no significant effect on early-late tracheostomy rates, length of stay in the ICU, and mortality. During the pandemic, there was a significant difference in mortality among patients with cranial pathology.
Conclusion: Early tracheostomy application decreased the length of ICU stay but did not significantly affect mortality. In addition, we found that the COVID-19 pandemic did not significantly affect mortality, except for early-late tracheostomy rates and patients with cranial pathology.
Keywords: Tracheostomy, COVID-19, intensive care unit, intubation, mortality

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVID-19) pandemisi ile birlikte optimum trakeostomi zamanı önemli hale gelmiştir. Bu çalışmanın amacı, COVID-19 pandemisinden önceki ve sonraki 4 yıllık süreçte tersiyer bir merkezin yoğun bakım ünitesinde (YBÜ) gerçekleştirilen erken ve geç trakeostomi uygulamalarının hasta sonuçları ve mortalite üzerine etkisini araştırmaktır.
Gereç ve Yöntem: Retrospektif kesitsel olan bu çalışmaya Mart 2018 ile Mart 2022 tarihleri arasında YBÜ'de perkütan trakeostomi açılan hastalar dahil edildi. Hastalar Grup 1 (erken <10 gün) ve Grup 2 (geç ≥10 gün) olarak sınıflandırılarak COVID-19 pandemisi öncesi ve sonrası dönemler halinde değerlendirildi. Hastaların demografik verileri, klinik özellikleri ve mortaliteleri analiz edildi.
Bulgular: Perkütan trakeostomi açılan 137 hasta çalışmaya dahil edildi. Tüm popülasyonun %62'si erkekti ve %29,1'ine erken trakeostomi uygulandığı saptandı. Grup 1'deki hastaların yaş ortalaması ve YBÜ'de kalış süresi anlamlı olarak düşük olmakla birlikte gruplar arasında mortalite açısından anlamlı farklılık saptanmadı. Pandemi öncesinde trakeostomi açılan hastaların en sık YBÜ'ye yatış endikasyonu kraniyal patolojiler iken pandemi döneminde COVID-19 idi. COVID-19 pandemisinin, erken-geç trakeostomi oranları, YBÜ'de kalış süresi ve mortalite üzerine anlamlı etkisi saptanmadı. Pandemi döneminde sadece kraniyal patolojili hastaların mortalitelerinde anlamlı farklılık mevcuttu.
Sonuç: Bu çalışmada erken trakeostomi uygulamasının YBÜ kalış süresini azaltmakla birlikte mortalite üzerine anlamlı etki yapmadığı saptandı. Ek olarak COVID-19 pandemisinin, erken-geç trakeostomi oranları ve kraniyal patolojili hastalar dışında mortalite üzerinde anlamlı etki yapmadığını saptadık.
Anahtar Kelimeler: Trakeostomi, COVID-19, yoğun bakım ünitesi, entübasyon, mortalite

Introduction

A tracheostomy is the opening of the tracheal ostium to the skin by creating an opening in the anterior wall of the trachea. With the development of percutaneous techniques, it has become a frequently applied procedure in intensive care unit (ICU) patients. Long-term respiratory failure, decreased level of consciousness, loss of airway reflexes, and trauma are the most common indications for tracheostomy (1). It has advantages, such as ensuring airway safety, facilitating nursing care, aspiration of the respiratory tract, reducing the need for sedation, facilitating patient discharge from the ICU, allowing oral feeding, and enabling speech (2,3). There is no absolute consensus on the need for tracheostomy opening in patients who are followed up in the ICU. However, there is no agreed-upon time frame for defining tracheostomy as early or late (4).

As a cause of viral pneumonia, Coronavirus disease-2019 (COVID-19) causes prolonged hospitalizations, and mechanical ventilators are needed for various patient groups in the ICU (5,6). The incidence of acute hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS) in COVID-19 pneumonia has been reported in 17-29% (7). It has been reported that 10-15% of COVID-19 patients who develop ARDS need tracheostomy (8). Although some guidelines do not recommend early tracheostomy in patients with COVID-19, it has been reported to be safe (9,10).

This study aimed to investigate the effects of early and late tracheostomy procedures performed in the ICU of a tertiary center on patient outcomes and mortality during the four years before and after the COVID-19 pandemic.

Materials and Methods

Ethics committee approval was obtained from the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee for this retrospective cross-sectional study (date: 30.06.2021, number: 200). The study was initiated in accordance with the principles of the Declaration of Helsinki. Percutaneous tracheostomy procedures were performed in the ICU of University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (ICU) before and after the COVID-19 pandemic for four years (01.03.2018-01.03.2022). The data were reviewed retrospectively using the hospital information system.

Before the COVID-19 pandemic, an ICU service with 36 beds was provided by our hospital's anesthesiology and reanimation clinic. As a result of the increasing need for beds after the pandemic, a new ICU was established, and ICU services were provided to patients with 50 beds. In this descriptive study, a sample size was not chosen. All patients who underwent percutaneous tracheostomy in the ICU within the last 4 years between the relevant dates were included in the study. The current study did not include patients who underwent surgical tracheostomy procedures in the operating room and were previously tracheotomized.

Demographic data of patients, indications for admission to ICUs, comorbidities, tracheostomy opening times, length of stay in ICU, length of stay on mechanical ventilator after tracheostomy, acute physiology and chronic health assessment-2 scores during hospitalization, discharge status (palliative care, home, inpatient service), and 90-day mortality were investigated. The patients were analyzed by classifying them as Group 1 (early <10 days, before ICU hospitalization reached ten days) and Group 2 (late ≥10 days, and tracheostomy opened after 10 days of ICU admission) according to the time of tracheostomy. In addition, early-late tracheostomy applications performed during the pre- and post-pandemic periods were analyzed. To provide standardization in the diagnosis of admission to the ICU, patients were divided into groups with cranial pathologies and those with respiratory pathologies and analyzed in the pre- and post-pandemic periods. Epidural, subdural, intracranial hemorrhages, traumatic brain injuries, and stroke were considered cranial pathologies. Pneumonia, other conditions causing respiratory failure, sepsis, and COVID-19 were accepted as respiratory pathologies.

Statistical Analysis

The SPSS 29.0 program (SPSS Inc., Chicago, USA) was used to analyze the data. Data are expressed as mean standard deviation, number of patients (n), and percentage. The conformity of the variables to the normal distribution was evaluated analytically (Shapiro-Wilks test) and visually (histogram). The independent sample t-test was used to analyze quantitative data with normal distribution among the groups, and the Mann-Whitney U test was used to analyze quantitative variables that did not show normal distribution. The Pearson chi-square and Fisher's exact tests were used to evaluate qualitative data. The statistical significance limit was accepted as $p<0.05$.

Results

A total of 137 patients who underwent percutaneous tracheostomy during the four years before and after the COVID-19 pandemic in the ICU were included in the study. Between the relevant dates, eight patients were found to have undergone surgical tracheotomy for various reasons (such as neck trauma and complicated head-neck structure), and these patients were not included in the study. There were 62% (n=85) men in the study population, and the mean age was 62.2±18.3 years. Early tracheostomy was found in 29.1% (n=40) of all tracheostomy (Group 1). The mean age and length of stay in the ICU of patients who underwent early tracheostomy were significantly lower than those who underwent late tracheostomy (p=0.006 and p<0.001, respectively). However, early and late tracheostomy applications did not significantly affect discharge and mortality in the entire population (p=0.844 and p=0.969, respectively) (Table 1).

When tracheostomy applications were analyzed by dividing them into pre- and post-COVID-19 periods, 37.9% (n=52) of tracheostomy were performed before and 62.1% (n=71) during the pandemic. Although 0.72 (52/36/2) tracheostomy were performed per bed per year before the pandemic, it was found that 0.85 (85/50/2) tracheostomy per bed per year during the pandemic period. There was no significant difference in the number of patients who underwent early and late tracheostomy according to the periods (p=0.398). Although the discharge rates were lower in patients with tracheostomy during the pandemic, no significant difference was found (38.8% vs. 51.9%, p=0.134). Similarly, although mortality rates were higher during the pandemic, no significant difference was found (60% vs. 46.1%, p=0.114) (Table 2).

Considering the indications for admission to the ICU of patients who underwent tracheostomy, cranial pathologies (epidural, subdural, intracranial hemorrhages, and traumatic brain injury) were observed most frequently before the pandemic. At the same time, COVID-19 was detected most frequently during the pandemic period (Table 3).

Tracheostomy was performed in 27% (n=37) of the patients due to cranial pathologies. All patients with cranial pathology during the pandemic were COVID-19-negative. In these patients, no significant difference was found between the early and late tracheostomy rates between the periods (p= 0.488). The discharge rate was significantly lower in patients with cranial pathology during the pandemic period

Table 1. Demographic data and some clinical characteristics of the entire population before and after COVID-19

Variable	All populations (n=137)	Group 1 Early tracheostomy (n=40)	Group 2 Late tracheostomy (n=97)	p-value
Age (years)	62.2±18.3	55.318.6±	65.1±17.6	**0.006**
Sex, n (%)				0.105
Female	52 (37.9)	11 (27.5)	41 (42.2)	
Male	85 (62.0)	29 (72.5)	56 (57.7)	
Comorbity, n (%)	102 (74.4)	26 (65.0)	76 (78.3)	0.103
Intubation time (days)	17.7±13.7	6.3±1.9	22.3±13.8	**<0.001**
APACHE-2 score	24.6±9.5	25.7±9.0	24.2±9.7	0.304
Duration of ICU (days)	44.8±28.8	29.6±18.2	51.2±30.0	**<0.001**
Duration of Mv after tracheostomy (days)	21.7±17.2	19.5±15.8	22.7±17.8	0.162
Discharge, n (%)	60 (43.7)	17 (42.5)	43 (44.3)	0.844
Place of discharge, n (%)				0.568
Palliative care center	39 (28.4)	12 (30.0)	27 (27.8)	
To home	21 (15.3)	5 (12.5)	16 (16.4)	
Mortality (90-day), n (%)	75 (54.7)	22 (55.0)	53 (54.6)	0.969

The values are the number of patients (n), percentage, mean, and standard deviation.
ICU: Intensive care unit, APACHE-2: acute physiology and chronic health assessment-2, Mv: mechanical ventilation, COVID-19: coronavirus disease-2019

Table 2. Characteristics of patients tracheotomized before and after the COVID-19 pandemic			
Variable	**Pre-pandemic period (n=52)**	**Pandemic period (n=85)**	**p-value**
Age (years)	64.7±20.3	60.6±17.0	0.115
Sex, n (%)			0.412
Female	22 (42.3)	30 (31.8)	
Male	30 (57.7)	55 (68.2)	
Tracheostomy group			0.398
Early (<10 days)	13 (25.0)	27 (23.1)	
Late (≥10 days)	39 (75.0)	58 (76.9)	
Intubation time (days)	15.8±8.7	18.8±16.0	0.817
Comorbity, n (%)	38 (73.1)	64 (75.3)	0.773
APACHE-2 score	27.0±11.2	23.1±8.0	0.087
Duration of ICU (days)	44.4±21.8	45.1±32.5	0.618
Duration of Mv after tracheostomy (days)	22.6±16.3	21.2±17.9	0.335
Discharge, n (%)	27 (51.9)	33 (38.8)	0.134
Mortality (90-day), n (%)	24 (46.1)	51 (60.0)	0.114

The values are the number of patients (n), percentage, mean, and standard deviation.
ICU: Intensive care unit, APACHE-2: acute physiology and chronic health assessment-2, Mv: mechanical ventilation, COVID-19: coronavirus disease-2019

Table 3. ICU admission diagnoses before and after the COVID-19 pandemic	
Before the COVID-19 pandemic (n=52)	COVID-19 pandemic (n=85)
Epidural, subdural, intracranial hemorrhages, and traumatic brain injury (n=16)	COVID-19 (n=26)
	Epidural, subdural, intracranial hemorrhages, and traumatic brain injury (n=9)
Respiratory failure and pneumonia (n=13)	Non-COVID-19 respiratory failure and pneumonia (n=12)
Ischemic or hemorrhagic strokes (n=6)	Postoperative follow-up (n=10)
Postoperative follow-up (n=5)	Ischemic or hemorrhagic strokes (n=6)
Others* (n=12)	Others* (n=31)

Values were expressed as the number of patients, ICU: Intensive care unit, *: falls, traffic accidents, intoxication, malignancies, suicide, pancreatitis, assault, status epilepticus, COVID-19: coronavirus disease-2019

(26.7% vs. 72.7%, p=0.006). Similarly, 90-day mortality rates were significantly higher during the pandemic (73.3% vs. 22.7%, p=0.002) (Table 4).

Tracheostomy was performed in 43.7% (n=60) of the patients due to respiratory pathologies. The mean age of the patients during the pandemic period was significantly lower than that before the pandemic (62.2±15.4 vs. 75.4±12.4, p=0.004). There was no significant difference in the early tracheostomy and mortality rates between the pandemic and the pre-pandemic period (Table 5).

Discussion

In this study, which examined tracheostomy patients in the ICU during the four years before and after the COVID-19 pandemic, early tracheostomy was performed in approximately 29% of the entire population, and the mean age and length of stay in the ICU were shorter in this group of patients. In addition, early tracheostomy did not have a significant effect on discharge and mortality. The COVID-19 pandemic did not affect early-to-late tracheostomy rates. In addition, the COVID-19 pandemic did not significantly affect

Table 4. Clinical characteristics of patients who underwent tracheostomy due to cranial pathologies before and after the COVID-19 pandemic

Variable	Pre-pandemic period (n=22)	Pandemic period (n=15)	p-value
Age (years)	63.3±21.3	64.5±17.5	0.862
Sex, n (%)			0.191
Female	7 (31.8)	8 (53.3)	
Male	15 (68.2)	7 (46.7)	
Tracheostomy group			0.488
Early (<10 days)	6 (27.3)	6 (40)	
Late (≥10 days)	16 (72.7)	9 (60)	
Intubation time (days)	14.3±7.5	14.2±7.8	0.867
Comorbity, n (%)	14 (63.6)	11 (73.3)	0.724
APACHE-2 score	27±13.2	23.2±7.8	0.314
Duration of ICU (days)	47.9±25.8	41.6±24.7	0.276
Duration of Mv after tracheostomy	25.8±19	24.1±24.1	0.350
Discharge, n (%)	16 (72.7)	4 (26.7)	**0.006**
Mortality (90-day), n (%)	5 (22.7)	11 (73.3)	0.002

The values are the number of patients (n), percentage, mean, and standard deviation. ICU: Intensive care unit, APACHE-2: acute physiology and chronic health assessment-2, Mv: mechanical ventilation, *: epidural, subdural, intracranial hemorrhages, traumatic brain injury, stroke, COVID-19: coronavirus disease-2019

Table 5. Clinical characteristics of patients who underwent tracheostomy due to respiratory pathologies before and after the COVID-19 pandemic

Variable	Pre-pandemic period (n=15)	Pandemic period (n=45)	p-value
Age (years)	75.4±12.4	62.2±15.4	**0.004**
Sex, n (%)			0.764
Female	7 (46.7)	19 (42.2)	
Male	8 (53.3)	26 (57.8)	
Tracheostomy group			1.000
Early (<10 days)	2 (13.3)	8 (17.8)	
Late (≥10 days)	13 (86.7)	37 (82.2)	
Intubation time (days)	18.7±8.9	22±15.8	0.745
Comorbity, n (%)	15 (100)	36 (85)	0.095
APACHE-2 score	28.1±10.6	21.9±7.8	**0.020**
Duration of ICU (days)	42.8±16.5	45.6±22	0.649
Duration of Mv after tracheostomy (days)	19±14.2	18.8±13.8	1.000
Discharge, n (%)	8 (53.3)	19 (42.2)	0.454
Mortality (90-day), n (%)	7 (46.7)	26 (57.8)	0.454

The values are the number of patients (n), percentage, mean, and standard deviation.
ICU: Intensive care unit, APACHE-2: acute physiology and chronic health assessment-2, Mv: mechanical ventilation, *: pneumonia, other respiratory problems, and COVID-19, COVID-19: coronavirus disease-2019

mortality, except in tracheotomized patients due to cranial pathologies.

It has been reported that the mean age of patients who underwent tracheotomy in the ICU during the COVID-19 pandemic was lower than during the pre-pandemic period (11). Another study reported that more tracheostomy were opened in men during the pandemic period than before the COVID-19 pandemic (12). The authors stated that the more severe course of COVID-19 in men led to this situation. Consistent with the literature, in our study, more tracheostomy were performed in the entire population and men during COVID-19. Similarly, the mean age of patients during the pandemic period was lower than that during the pre-pandemic period, although this difference was not significant. We believe that this is because the severe course of COVID-19 in young people, especially men, causes prolonged hospitalization in the ICU and the need for tracheostomy.

The literature has not agreed on the optimum tracheostomy time and the early and late definitions of tracheostomy. Edipoğlu et al. (4) reported that early (≤10 days mechanical ventilation) and late (>10 days) tracheostomy results were performed in 65% of the patients, and mortality was high in the late tracheostomy group. However, it was not significant. A Cochrane review of 8 studies, including 1977 patients, examined the outcomes of early (≤10 days mechanical ventilation) and late (>10 days) tracheostomy. The authors reported that although lower mortality was reported in the early tracheostomy group, with a risk ratio of 0.83, no high-quality evidence was available for specific subgroups (13). However, some studies have also reported that opening of a tracheostomy or the time of tracheostomy does not affect mortality in patients who are followed up in the ICU (14-16). With the COVID-19 pandemic, the question of when to open a tracheostomy has become more critical. Guidelines do not recommend tracheostomy within the first 2 weeks of intubation to reduce viral load in patients intubated due to COVID-19 and expose healthcare workers to less risk of aerosol transmission (17). However, it has been stated that the tracheostomy can be opened safely without waiting 2-3 weeks with appropriate personal protective equipment and a modified percutaneous dilatational tracheostomy technique (18). Chao et al. (12) reported that the mean number of days to be intubated until tracheostomy in COVID-19 patients was 19±6 days. Another study reported that the number of intubated days until tracheotomy was significantly higher (19±7 vs. 23±5 days) in patients with COVID-19 (11). In our study, the number of intubated days until tracheostomy was found to be high (18.8± 16 vs. 15.8± 8.7), although it was not significant in the COVID-19 period.

The diagnosis and clinical condition of patients are essential in the decision to perform tracheostomy in ICUs. It is recommended that the tracheostomy be opened quickly in patients who are not expected to be extubated within a short time (such as central nervous system pathologies, neuromuscular diseases, and medulla spinalis injuries). In cases in which the course of the disease cannot be predicted precisely, such as moderate cerebral damage, neuromuscular diseases with attacks, and moderate to severe chronic lung pathologies, the decision for tracheostomy can be difficult. Studies conducted in Turkey before the COVID-19 pandemic reported that tracheostomy was most frequently performed due to central nervous system pathologies (2,19,20). Another study from Turkey reported that 24.2% of tracheostomy procedures during the pandemic were due to COVID-19. A study from the USA reported that tracheostomy was most frequently performed due to ARDS in patients with COVID-19 (12). Consistent with the literature, in our study, tracheostomy was performed most frequently (30.7%) in the pre-pandemic period due to central nervous system pathologies (epidural, subdural, intracranial hemorrhages, traumatic brain injury, and strokes) and most frequently (30.5%) in the pandemic period due to COVID-19. In our study, the mortality rate of patients with cranial pathologies was significantly higher during the pandemic than before the pandemic (73.3% vs. 22.7%). All patients with cranial pathology during the COVID-19 period were negative for COVID-19. The high mortality rate may be due to late hospital admissions and the regulations in health systems during the pandemic period. There was no significant increase in the mortality rate of patients who underwent tracheostomy due to respiratory problems during the pandemic. It has been reported that early tracheostomy reduces the length of stay in the ICU, the length of stay with a mechanical ventilator, and the need for sedation, but it has no effect on mortality (4,21,22). The tracheostomy management in critical care (Trac-Man) study reported that early tracheostomy (first 1-4 days) did not affect mortality and length of stay in the ICU (23). In our study, although the duration of stay in the ICU was significantly lower in patients with early tracheostomy than in the entire population, no significant difference was observed in the 90-day mortality rates.

Study Limitations

The main limitations of this study are its single-center, retrospective design, and the relatively low number of cases. In addition, early-late complications related to tracheostomy were not examined.

Conclusion

In conclusion, considering all patients before and after the pandemic, early tracheostomy did not significantly affect mortality, although it shortened the ICU stay. In addition, the COVID-19 pandemic did not cause significant changes in the rates of early- to late tracheostomy. There was a significant increase in the mortality rate of patients who underwent tracheostomy in the ICU due to cranial pathologies only during the pandemic. In similar pandemics that we will encounter, tracheostomy can be performed healthily without getting stuck in timing.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee for this retrospective cross-sectional study (date: 30.06.2021, number: 200). The study was initiated in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., A.S.Ş., Design: K.A., A.S.Ş., Data Collection or Processing: K.A., Analysis or Interpretation: K.A., A.S.Ş., Literature Search: K.A., Writing: K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Durbin CG Jr.Tracheostomy: why, when, and how?. Respir Care. 2010;55:1056-68.
2. Kırca H, Çakın Ö, Cengiz M, Yılmaz M, Ramazanoğlu A. Yoğun Bakımda Trakeotomi: Endikasyonlar, Komplikasyonlar ve Prognoz. Turk J Intense Care. 2018;16:17-25.
3. Groves DS, Durbin CG Jr. Tracheostomy in the critically ill: indications, timing and techniques. Curr Opin Crit Care. 2007;13:90-7.
4. Edipoğlu İS, Özcan PE, Akıncı İÖ, Yornuk M, Orhun G, Şentürk E, et al. Assessment of Early and Late Tracheostomy Interventions in Intensive Care Patients. Turk J Intensive Care. 2013;11:60-3.
5. Arslan K, Arslan HC, Sahin AS. Evaluation of critically ill obstet¬ric patients treated in an ıntensive care unit during the COVID-19 pandemic. Ann Saudi Med. 2023;43:10-6.
6. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
7. Goh KJ, Choong MCM, Cheong EHT, Kalimuddin S, Duu Wen S, Phua GC, et al. Rapid progression to acute respiratory distress syndrome: Review of current understanding of critical ıllness from coronavirus disease 2019 (COVID-19) infection. Ann Acad Med Singapore. 2020;49:108-18.
8. Şahin AS, Kaya E. COVID-19 Hastalarında Perkütan Trakeostomi. İKSSTD. 2021;13:160-1.
9. Arslan K. COVID-19 Pandemisi Döneminde Yoğun Bakım Ünitesinde Trakeostomi Uygulamaları. In: Özcengiz D editor. Güncel Anesteziyoloji ve Ağrı Çalışmaları V. Ankara: Akademisyen Kitabevi; 2022. p. 71-6.
10. Avilés-Jurado FX, Prieto-Alhambra D, González-Sánchez N, de Ossó J, Arancibia C, Rojas-Lechuga MJ, et al. Timing, Complications, and Safety of Tracheotomy in Critically Ill Patients With COVID-19. JAMA Otolaryngol Head Neck Surg. 2020;147:1-8.
11. Yücedağ F, Kahraman ŞŞ. COVID-19 Pandemi Öncesi ve Pandemi Döneminde Trakeotomi Sonuçlarının Karşılaştırılması. Selcuk Med J. 2022;33:71-5.
12. Chao TN, Harbison SP, Braslow BM, Hutchinson CT, Rajasekaran K, Go BC, et al. Outcomes After Tracheostomy in COVID-19 Patients. Ann Surg. 2020;272:e181-6.
13. Ghattas C, Alsunaid S, Pickering EM, Holden VK. State of the art: percutaneous tracheostomy in the intensive care unit. J Thorac Dis. 2021;13:5261-76.
14. Dochi H, Nojima M, Matsumura M, Cammack I, Furuta Y. Effect of early tracheostomy in mechanically ventilated patients. Laryngoscope Investig Otolaryngol. 2019;4:292-9.
15. Siempos II, Ntaidou TK, Filippidis FT, Choi AMK. Effect of early versus late or no tracheostomy on mortality and pneumonia of critically ill patients receiving mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med. 2015;3:150-8.
16. Arslan K, Şahin AS, Yalçın N, Kaya E. Evaluation of Trauma Patients Followed Up and Treated in Intensive Care Unit: The Sample of İstanbul Province Training and Research Hospital. Turk J Intensive Care. 2023;21:41-7.

17. Miles BA, Schiff B, Ganly I, Ow T, Cohen E, Genden E, et al. Tracheostomy during SARS CoV- 2 pandemic: recommendations from the New York Head and Neck Society. Head Neck. 2020;42:1282-90.
18. Angel L, Kon ZN, Chang SH, Rafeq S, Palasamudram Shekar S, Mitzman B, et al. Novel Percutaneous Tracheostomy for Critically Ill Patients With COVID-19. Ann Thorac Surg. 2020;110:1006-11.
19. Yeşiler Fİ, Şendur ÜG. Our Experiences Of Tracheostomy In Intensive Care Unit. Aegean J Med Sci. 2018;1:106-10.
20. Şeker YT, Tülübaş EK, Hergünsel O, Çukurova Z. Evaluation of late term complications dilatation tracheostomy of intensive care unit. Med J Bakirkoy. 2017;13:170-4.
21. Terragni PP, Antonelli M, Fumagalli R, Faggiano C, Berardino M, Pallavicini FB, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: A randomized controlled trial. JAMA. 2010;303:1483-9.
22. Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. BMJ. 2005;330:1243.
23. Young D, Harrison DA, Cuthbertson BH, Rowan K; TracMan Collaborators. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. JAMA. 2013;309:2121-9.

Turk J Intensive Care 2024;22:256-63
DOI: 10.4274/tybd.galenos.2023.27136

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Ekin Soydan,
Gökhan Ceylan,
Gülhan Atakul,
Sevgi Topal,
Mustafa Çolak,
Pınar Hepduman,
Özlem Saraç Sandal,
Ferhat Sarı,
Utku Karaarslan,
Hasan Agin

Relationship Between Driving Pressure During the First 24 Hours and Mortality Among Pediatric Critical Care Patients

Pediatrik Yoğun Bakım Hastalarında ilk 24 Saatte Ölçülen Sürüş Basıncı ile Mortalite Arasındaki Ilişki

Received/Geliş Tarihi : 19.04.2023
Accepted/Kabul Tarihi : 24.10.2023

Ekin Soydan, Gökhan Ceylan, Gülhan Atakul, Sevgi Topal, Mustafa Çolak, Pınar Hepduman, Özlem Saraç Sandal, Ferhat Sarı, Utku Karaarslan, Hasan Agin

University of Health Sciences Turkey Dr. Behçet Uz Pediatric Diseases and Sugery Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey

Ekin Soydan MD (✉),
University of Health Sciences Turkey Dr. Behçet Uz Pediatric Diseases and Sugery Training and Research Hospital, Clinic of Pediatric Intensive Care Unit, İstanbul, Turkey

E-mail : dr-ekinsoydan@hotmail.com
ORCID ID : orcid.org/0000-0003-2626-5499

ABSTRACT *Objective:* Respiratory failure is one of the most common causes of mortality in pediatric intensive care unit patients. Adult and a small number of pediatric studies have also associated driving pressure with mortality in acute respiratory distress syndrome (ARDS) patients, but studies showing the relationship between driving pressure and mortality in patients without ARDS are inconsistent and limited. This study aimed to determine whether driving pressure was associated with mortality in pediatric patients diagnosed as pediatric ARDS (pARDS) and non-pARDS who received mechanical ventilation support due to respiratory failure.
Materials and Methods: Mechanically ventilated patients were recorded if the foreseen ventilation duration was more than 24 hours. Driving pressure and other ventilator parameters of patients in the pARDS and non-pARDS groups were compared with their 30-day mortality.
Results: A total of 116 children were included in our study. Thirty-four patients were classified in pARDS group, whereas 82 patients werein non-PARDS group. All patients' first day of mechanical ventilation parameters [ΔP (p<0.001), PIP (p<0.001), Pplat (p<0.001), P_{mean} (p=0.008), Cstat (p<0.001), Cstat/body weight (p<0.001), FiO_2 (p=0.001)] werefound to be associated with hospital mortality. Driving pressure and other ventilator parameters associated with mortality in the univariate analysis were further evaluated by logistic regression analysis and driving pressure was determined as the most associated ventilator parameter with mortality [odds ratio (OR)=1.51, 95% confidence interval (CI) 1.24 to 1.82, p≤0.001]. We assessed independently the relationship between ΔP and mortality in patients non-pARDS and pARDS and we found ΔP was related to mortality in both patients (OR=1.59, 95% CI 1.06 to 2.36, p<0.022) and non-ARDS patients (OR=1.47, 95% CI 1.09 to 1.98, p<0.010). We identified a driving pressure cut-off value of 14.5 cm H_2O for all patient groups.
Conclusion: Driving pressure was significantly associated with an increased risk of mortality among mechanically ventilated both pARDS and non-pARDS patients.
Keywords: Driving pressure, pediatric intensive care unit, mortality, pediatric acute respiratory distress syndrome

ÖZ *Amaç:* Solunum yetmezliği, çocuk yoğun bakım ünitesi hastalarında en sık ölüm nedenlerinden biridir. Yetişkin ve az sayıda pediatrik çalışmada akut solunum distresi sendromu (ARDS) hastalarında sürüş baskısı ile mortaliteyi ilişkilendirmiştir, ancak ARDS'si olmayan hastalarda sürüş basıncı ile mortalite arasındaki ilişkiyi gösteren çalışmalar tutarsız ve sınırlıdır. Bu çalışmada solunum yetmezliği nedeniyle mekanik ventilasyon desteği alan pediatrik ARDS (pARDS) ve non-pARDS tanılı pediatrik hastalarda sürüş basıncının mortalite ile ilişkisinin belirlenmesi amaçlandı.
Gereç ve Yöntem: Öngörülen ventilasyon süresi 24 saatten fazla mekanik ventilasyon uygulanan hastalar kaydedildi. pARDS ve non-PARDS gruplarındaki hastaların sürüş basıncı ve diğer ventilatör parametreleri 30 günlük mortaliteleri ile karşılaştırıldı.
Bulgular: Çalışmamıza toplam 116 çocuk dahil edildi. Otuz dört hasta pARDS grubunda sınıflandırılırken, 82 hasta PARDS dışı gruptaydı. Tüm hastaların mekanik ventilasyonun ilk günü parametreleri [ΔP (p<0,001), PIP (p<0,001), Pplat (p<0,001), P_{mean} (p=0,008), Cstat (p<0,001), Cstat/vücut ağırlığı (p<0,001), FiO_2 (p=0,001)] hastane mortalitesi ile ilişkili bulunmuştur. Tek değişkenli analizde mortalite ile ilişkilendirilen sürüş basıncı ve diğer ventilatör parametreleri, lojistik regresyon analizi ile ayrıca değerlendirildi ve sürüş basıncı, mortalite ile en ilişkili ventilatör parametresi olarak belirlendi [olasılık oranı (OR)=1,51, %95 güven aralığı (GA) 1,24-1,82, p≤0,001]. pARDS ve pARDS

olmayan hastalarda ΔP ile mortalite arasındaki ilişkiyi bağımsız olarak değerlendirdik ve ΔP'nin hem PARDS hastalarında (OR=1,59, %95 GA 1,06-2,36, p<0,022) hem de non-PARDS hastalarda mortalite ile ilişkili olduğunu bulduk (OR=1,47, %95 GA 1,09-1,98, p<0,010). Tüm hasta grupları için 14,5 cm H_2O'luk bir sürüş basıncı kesme değeri belirledik.
Sonuç: Sürüş basıncı, mekanik olarak ventile edilen hem pARDS hem de pARDS olmayan hastalarda artan mortalite riski ile anlamlı şekilde ilişkiliydi.
Anahtar Kelimeler: Sürüş basıncı, pediatrik yoğun bakım ünitesi, mortalite, pediatrik akut solunum sıkıntısı sendromu

Introduction

Respiratory failure is one of the most common causes of hospitalization and mortality in patients in the pediatric intensive care unit (PICU). Although positive pressure mechanical ventilation is a life-saving treatment, it is associated with risks of morbidity and mortality. Although there is a consensus on mechanical ventilation in adult patients, this knowledge should be reflected in concrete data for the pediatric population (1-4). Mechanical ventilation with high tidal volumes may damage the lung through alveolar overdistension (volutrauma and barotrauma) and by causing the release of inflammatory cytokines (biotrauma) into the systemic circulation (5,6). Recently, it has been suggested to target driving pressure (ΔP) in ARDS patients to achieve improved outcomes with optimal mechanical ventilation (7-10). ΔP is calculated as the difference between the Plateau pressure (Pplat) and positive end-expiratory pressure (PEEP) and is derived by dividing tidal volume by respiratory system compliance (ΔP=Pplat-PEEP). This measure estimates the mechanical strain (dynamic strain) caused by lung tidal volume. It is a non-invasive, straightforward method that can be easily performed at the bedside (10-12). Numerous studies have found an association between higher ΔP values and increased mortality in adults with ARDS. However, studies examining the relationship between driving pressure and mortality in patients with non-ARDS are limited, and the results have been contradictory (13-18).

This study investigates whether ΔP is associated with mortality in pediatric patients diagnosed with pARDS and non-pARDS who received mechanical ventilation support due to respiratory failure.

Materials and methods

This prospective, single-center observational study included patients admitted to the PICU. The study protocol was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (decision no: 2020/07-02, date: 07.05.2020). Written informed consent was obtained from the parents/caregivers after the patient's initial clinical stabilization period. The study included patients aged between 1 month and 18 years who required invasive mechanical ventilation support due to respiratory failure in the PICU and were admitted between March 2018 and April 2020. Patients were excluded if they received ventilation via a tracheostomy cannula or if they were extubated or died within the first 24 hours of ventilation.

Only patients who received at least 24 hours of mechanical ventilation were included in the analysis. Patients were divided into two groups based on the oxygenation index (OI), calculated using the formula: [mean airway pressure (MAP)xfraction of inspired oxygen (FiO_2)]/partial pressure of oxygen in arterial blood (PaO_2)x100, by the pediatric acute lung injury and sepsis consensus conference (PALICC) criteria for defining ARDS and non-ARDS. The PARDS definition was similarly based on the PALICC guidelines (3). On day 1, data were prospectively recorded, including patient demographics, ventilator settings (VT, VT/ideal body weight [IBW], respiratory rate, peak inspiratory pressure [PIP], Pplat, MAP [P_{mean}], minute volume, PEEP, static compliance [Cstat], FiO_2, inspiratory time, and expiratory time). Additionally, the OI, Cstat (VT/ΔP), PaO_2/FiO_2 ratio, driving pressure (ΔP), PRISM III score, and pediatric sequential organ failure assessment (pSOFA) scores were calculated.

All patients were ventilated in pressure control mode throughout their hospitalization. Ventilator data were recorded twice within each 24 hours. Driving pressure was measured by obtaining Pplat every 12 hours using an inspiratory hold maneuver, with the mean Pplat value calculated from two measurements within 24 hours.

Total PEEP was measured using an expiratory hold maneuver, with the mean total PEEP value also calculated from two measurements within 24 hours; ΔP was then calculated using the formula Pplat PEEP. Neuromuscular blocking agents were administered to all patients before the measurements. Each patient was monitored for up to 30 days or until hospital discharge. ΔP was compared with

other mechanical ventilator parameters between survivors and non-survivors at day 30, and ΔP and other parameters were also compared between the ARDS and non-ARDS groups based on 30-day mortality outcomes.

Statistical Analysis

Our primary objective was to assess the association between ΔP and mortality in patients with ARDS and non-ARDS. Second, we aimed to analyze the relationship between mortality and ΔP along with other mechanical ventilation parameters. Comparisons of driving pressure and other lung dynamics, depending on the data type and distribution, were conducted using the chi-square test, Wilcoxon's independent t-test, or Mann-Whitney U test, with a p-value of <0.05 as statistically significant. The correlation coefficient was used to gauge the strength of the associations between variables. Pearson's correlation was applied for parametric data and Spearman's correlation for non-parametric data to identify covariances before logistic regression. Spearman's correlation analysis was used to detect covariances.

Variables found to have significant associations with mortality in univariate analyses were further assessed by logistic regression [reporting odds ratio (OR) and 95% confidence intervals (CI)]. Model adequacy was evaluated with Hosmer-Lemeshow goodness-of-fit statistics. The multivariable analyses identified covariates potentially related to mortality. We ensured that VT/IBW, PaO_2, OI, FiO_2, PRISM III score, days of ventilation, and pSOFA score were not collinear with ΔP. Pplat, PIP, and P_{mean} were excluded from logistic regression models containing ΔP due to concerns regarding collinearity. Separate models were generated for Pplat, PIP, and P_{mean} due to their collinearity with the driving pressure.

The final model was used to identify the most relevant parameter associated with 30- day mortality in patients receiving mechanical ventilation for respiratory failure. ΔP cut-off values in our study were classified, and mortality predictions were calculated using receiver operating characteristic analysis (19,20). All statistical data were analyzed using IBM SPSS Statistics for Windows, version 22 (Armonk, NY).

Results

Between March 2018 and April 2020, 263 patients received invasive mechanical ventilation support in our admitted to the PICU. However, 144 patients who did not meet the inclusion criteria were excluded from the study. A total of 116 children were included in the study. The median duration of mechanical ventilation was 7 days (IQR: 9-14 days). Sepsis (31.8%) was the most common reason for the need for mechanical ventilation. Followed by lower respiratory tract infection (28.4%). Thirty four patients were included in the pARDS group and 82 in the non-pARDS group. Patients with pARDS or non-pARDS had no statistically significant pSOFA values (p-value: 0.063), however, patients with pARDS had higher PRISM III scores (p-value<0.001) than non-pARDS patients (p<0.010). Characteristics were reported in (Table 1).

Among the included patients, 17 had mild, 9 had moderate, and 8 had severe pARDS. There were no differences in admission diagnosis and mortality on 30 days between the ARDS and non-ARDS groups. There were 93 survivors and 23 non-survivors at 30 days. The comparison between survivors and non-survivors at day 30 is shown in (Table 2).

All patients' mechanical ventilation parameters on the first day were [ΔP (p<0.001), PIP (p<0.001), Pplat (p<0.001), P_{mean} (p=0.008), Cstat (p<0.001), Cstat/IBW (p<0.001), FiO_2 (p=0.001)] associated with hospital mortality. OI, PaO_2, and days of ventilation were also associated with 30-day mortality in all patients (p<0.001, p=0.008, p=0.010, respectively). There was no significant association between VT/IBW (p=0.292), IT (p=0.986), ET (p=0.551), PEEP (p<0.221), RR (p=0.862), and 30- day mortality in all patients.

The primary regression model aimed to determine the effect of ΔP on 30- day mortality in all patients and the mechanical ventilator parameter most associated with 30- day mortality. Second, we aimed to determine the association of ΔP with 30- day mortality in patients with and without ARDS. As the collinearity between ΔP, PIP, Pplat, and P_{mean} was statistically significant, a logistic regression model was constructed for each of these variables (Table 3). ΔP was most associated with 30- day mortality (OR=1.51, 95% CI 1.24 to 1.82, p≤0.001). The P_{mean} was not associated with 30- day mortality in any of the patients (OR=1.31, 95% CI 0.98 to 1.73, p=0.062). We conducted separate analyses to determine the relationship between ΔP and mortality in patients with non-ARDS and ARDS, we found ΔP related to mortality in both patient groups (OR=1.59, 95% CI 1.06 to 2.36, p<0.022) and non-ARDS patients (OR=1.47, 95% CI 1.09 to 1.98, p<0.010) (Table 4).

Table 1. Demographic and clinical characteristics with pARDS and non-pARDS patients			
Characteristic	**pARDS patients (n=34)**	**non-pARDS patients (n=82)**	**p-value**
Age (months)	15.6 (9-35)	13.5 (7-24.4)	0.117
Female gender, n (%)	17.0 (50%)	34.0 (41.5%)	0.401
Days of ventilation	13.1 (8.6-17.0)	8.5 (6.3-12.1)	**0.010**
Admission diagnosis, n (%)			
Sepsis	12 (32.4%)	25 (30.5%)	
Pneumonia	10 (29.5%)	23 (28.1%)	
Neurological diseases	9 (26.5%)	25 (30.5%)	
Cardiological diseases	1 (2.9%)	3 (3.7%)	
Hematologic diseases	1 (2.9%)	2 (2.4%)	
Post-surgery	1 (2.9%)	2 (2.4%)	
Immun deficiency	1 (2.9%)	2 (2.4%)	
30-day mortality, (n) %	8 (23.5%)	15 (18.2%)	**<0.001**
pARDS n (%)			
Mild pARDS n (%)	17 (50.0%)		
Moderate pARDS n (%)	9 (26.5%)		
Severe pARDS n (%)	8 (23.5%)		

Parametric data are presented as mean±1 standard deviation or non-parametric data presented as median (first and third quartiles), pARDS: Acute respiratory distress syndrome

Table 2. Mechanical ventilator parameters and clinical findings of all patients according to hospital mortality			
Variable	**Survivors at day 30 (n=93)**	**Non-survivors at day 30 (n=23)**	**p-value**
VT (ml)	71.9 (51.3-108.5)	82.0 (61.5-120.9)	0.180
VT/IBW (mL/kg)	7.0 (6.0-8.1)	6.5 (5.0-9.0)	0.292
VE (L/min)	2.8 (2.1-4.1)	2.3 (1.7-3.8)	0.117
RR (bpm)	34.0 (34.0-40.0)	35.0 (30-42)	0.862
PIP (cm H_2O)	23.6 (19.5-26)	29.0 (25.0-34.0)	**<0.001**
P_{plat} (cm H_2O)	21.0 (19.0-25.0)	28.0 (24.0.-33.0)	**<0.001**
PEEP (cm H_2O)	7.0 (6.0-9.0)	7.0 (6.0-7.0)	0.221
ΔP (cm H_2O)	16.0 (13.0-18.0)	23.0 (19.0-26.0)	**<0.001**
P_{mean} (cm H_2O)	11.7 (10.3-13.6)	13.1 (12.2-18.2)	0.008
C_{stat} (mL/cmH_2O)	5.7 (3.5-8.1)	2.8 (2.0-5.7)	**<0.001**
Cstat/İBW (mL/cm H_2O/kg)	0.4 (0.3-0.6)	0.3 (0.2-0.4)	**<0.001**
IT (s)	0.6 (0.5-0.7)	0.6 (0.5-0.9)	0.986
ET (s)	1.1 (0.9-1.3)	1.1 (0.8-1.2)	0.551
FiO_2 (%)	35.0 (30.0-44.0)	40.0 (40.0-60.0)	0.001
OI	3.3 (2.5-3.7)	4.8 (3.2-12.1)	**<0.001**
$PaCO_2$ (mmHg)	48.0 (±6.7)	50.3 (±7.6)	0.225
$PaCO_2$, (mmHg)	122.3 (±26.4)	100.7 (±28.7)	0.008
Days of ventilation	10.5 (7.0-13.5)	8.0 (7.0-15.0)	0.010
PRISM III score	5.0 (2.3-8.8)	7.3 (2.0-10.0)	**<0.001**
pSOFA score	5.0 (4.0-7.0)	6.0 (5.0-9.0)	0.063

Parametric data are presented as mean±1 standard deviation or non-parametric data presented as median (first and third quartiles),VT: tidal volume, VT/İBW: tidal volume/ideal body weight, RR: Respiratory rate, PIP: Peak inspiratory pressure, Pplat: Plateau pressure, Pmean: Mean airway pressure, VE: minute volume, PEEP: Positive end-expiratory pressure, Cstat :static compliance, FIO_2: fraction of inspired oxygen, Is: İnspiratory time , ET: Expiratory time, OI:Oxygenation index, ΔP: driving pressure, Cstat: static compiance, PRISM III score: The pediatric index of mortality scores, MV: mechanical ventilator, PaO_2: partial pressure of oxygen

Table 3. Multivariable logistic regression model at hospital mortality for ΔP, PIP, P_{plat} and P_{mean}

MODEL 1			MODEL 2			MODEL 3			MODEL 4		
Variable	OR (95% CI)	p-value	Variable	OR (95% CI)	p-value	Variable	OR (95% CI)	p-value	Variable	OR (95% CI)	p-value
Age	1.01 (0.98-1.03)	0.304	**Age**	1.01(0.99-1.03)	0.313	**Age**	1.01 (0.98-1.03)	0.304	**Age**	1.00 (0.98-1.02)	0.494
Gender	0.16 (0.03-0.73)	0.018	**Gender**	0.28(0.06-0.85)	**0.028**	**Gender**	0.24 (0.86-1.06)	**0.030**	**Gender**	0.39 (0.12-1.22)	**0.018**
OI	0.68 (0.51-0.91)	0.011	**OI**	0.69 (0.52-0.92)	**0.011**	**OI**	0.68 (0.51-0.90)	**0.008**	**OI**	0.62 (0.42-0.91)	**0.014**
PaO_2	0.98 (0.95-1.01)	0.302	**PaO_2**	0.98 (0.95-1.01)	0.214	**PaO_2**	0.98 (0.95-1.00)	0.182	**PaO_2**	0.97 (0.94-1.00)	0.093
FiO_2	1.13 (1.01-1.27)	0.032	**FiO_2**	1.15 (1.03-1.28)	**0.010**	**FiO_2**	1.15 (1.03-1.28)	**0.011**	**FiO_2**	1.20 (1.07-1.35)	**0.001**
PRISM III	0.90 (0.77-1.05)	0.194	PRISM III	0.87 (0.76-1.01)	0.085	PRISM III	0.87 (0.76-1.01)	0.086	PRISM III	0.89 (0.77-1.03)	0.126
Day (MV)	0.90 (0.76-1.06)	0.901	Day (MV)	0.91 (0.78-1.05)	0.910	Day (MV)	0.90 (0.78-1.04)	0.184	Day (MV)	0.93 (0.82-1.05)	0.273
ΔP	1.51 (1.24-1.82)	<0.001	**PIP**	**1.26 (1.10-1.44)**	**0.028**	**P_{plato}**	**1.29 (1.12-1.50)**	**0.001**	**P_{mean}**	**1.31 (0.98-1.73)**	**0.062**

OR: Odd ratio, CI: confidence interval, FIO_2: fraction of inspired oxygen, OI:Oxygenation index Oİ, ΔP: driving pressure, PIP: Peak inspiratory pressure, Pplat: Plateau pressure, Pmean: Mean airway pressure, PRISM III score: The pediatric index of mortality scores, MV: mechanical ventilator, PaO_2: partial pressure of oxygen

Table 4. A multivariable logistic regression model with pARDS patients and non-pARDS patients for ΔP

pARDS Patients ΔP model			non-pARDS patients ΔP Model			All patients ΔP Model		
Variable	OR (95% C	p-value	Variable	OR (95% CI)	p-value	Variable	OR (95% CI)	p-value
Age	1.02 (0.98-1.06)	0.164	**Age**	0.96 (0.87-1.06)	0.482	**Age**	1.01 (0.98-1.03)	0.304
Gender	0.11 (0.00-1.74)	0.120	**Gender**	0.09 (0.00-1.00)	0.051	**Gender**	0.16 (0.03-0.73)	0.018
OI	0.68 (0.44-1.05)	0.084	**OI**	0.62 (0.04-9.01)	0.729	**OI**	0.68 (0.51-0.91**)**	**0.011**
PaO_2	1.05 (0.96-1.16)	0.255	**PaO_2**	0.97 (0.91-1.04)	0.255	**PaO_2**	0.98 (0.95-1.01)	0.302
FiO_2	1.16 (0.95-1.42)	0.144	**FiO_2**	1.14 (0.89-1.46)	0.145	**FiO_2**	1.13 (1.01-1.27)	**0.032**
PRISM III	0.90 (0.71-1.15)	0.429	PRISM III	0.81 (0.59-1.12)	0.217	PRISM III	0.90(0.77-1.05)	0.194
Day (MV)	0.83 (0.65-1.06)	0.143	Day (MV)	0.98 (0.77-1.25)	0.904	Day (MV)	0.90 (0.76-1.06)	0.901
ΔP	1.59 (1.06-2.36)	0.022	**ΔP**	**1.47 (1.09-1.98)**	**0.010**	**ΔP**	**1.51 (1.24-1.82)**	**<0.001**

OR: Odd ratio, CI: confidence interval, FIO_2: fraction of inspired oxygen, OI:Oxygenation index Oİ, ΔP: driving pressure, PIP: Peak inspiratory pressure, Pplat: Plateau pressure, Pmean: Mean airway pressure, PRISM III score: The pediatric index of mortality scores, MV: mechanical ventilator, PaO_2: partial pressure of oxygen

After evaluating the relationship between inspiratory airway pressures (ΔP, PIP, P_{mean}, Pplat) and 30- day mortality by logistic regression analysis, we also compared these 4 parameters with ROC analysis for ΔP area under the curve was 0.838 (95% CI, 0.738-0.939, p<0.001), Pplat 0.770 (95% CI, 0,662-0,878, p<0.001), PIP 0.762 (95% CI, 0.648-0.876, p<0.001) and P_{mean} 0.678 (95% CI, 0.558–0.798, p=0.008). When assessing the risk of death at each level of ΔP. We defined the cut-off value related to mortality in our study as 17 cm H_2O in patients with pARDS, 13 cm H_2O in patients without ARDS, and 14,5 cm H_2O in all patients. We found the overall mortality rate to be 10.2 times higher for patients with ΔP greater than 14.5 cm H_2O compared with patients whose ΔP was 14.5 cm H_2O (OR=10.2, 95% CI 1.37 to 70, 75, p<0.001).

Discussion

Mechanical ventilation remains one of the primary reasons for admission to admitted to the PICUs, with approximately 64% of admitted children requiring this intervention (21,22). Driving pressure (ΔP), calculated as the difference between end-inspiratory Pplat and applied PEEP, represents the ratio of tidal volume (VT) to respiratory system compliance. P has shown potential in reducing mortality among children receiving mechanical ventilation for respiratory failure. ΔP offers a simple, noninvasive approach and can be measured directly at the bedside.

In recent years, data from studies on adult ARDS have indicated that ΔP is strongly associated with mortality (10,23). Our study demonstrated that ΔP on day 1 was correlated with hospital mortality in patients with pARDS. Although the PALICC guidelines have not yet recommended targeting ΔP in patients with pARDS, the connection between ΔP and mortality in patients with ARDS is well established. However, this association remains unclear in patients without ARDS. A meta-analysis by Serpa Neto et al. (15) revealed increased postoperative lung complications with elevated ΔP during general anesthesia (24). In two previous studies, no significant relationship was observed between ΔP and mortality in non-ARDS patients (14,18). Our findings similarly indicate that ΔP on day 1 was related to 30-day mortality among non-pARDS patients receiving mechanical ventilation for respiratory failure. Mechanical ventilation was applied without targeting low tidal volume or specific ΔP values, suggesting that higher ΔP may increase the mortality risk in patients without ARDS due to elevated inspiratory pressures. Numerous recent studies highlight the significance of driving pressure on survival outcomes (25-29), and many ARDS studies have found associations between VT and mortality in pediatric patients (8,25,26). However, in our study, we observed no significant association between VT and mortality in pARDS and non-pARDS patients. This might explain the observed mortality association with ΔP and compliance in patients with pARDS.

Current adult ARDS data suggest that driving pressure is more closely associated with mortality than inspiratory pressure (10,23). Some pediatric studies have also identified linear correlations between mortality and PIP and Pplat (8,25). Higher inspiratory pressures (PIP, Pplat, P_{mean}, ΔP) were associated with 30- day mortality.

Using four distinct multivariate regression models, we found that ΔP had the strongest association with mortality. Each 1-SD increase in ΔP (approximately 7 cm H_2O) increased the mortality risk by 51% (10). ΔP cut-off values varied from 13 to 21 cm H_2O (10,27,28), and in our study, cut-offs were defined as 17 cm H_2O for patients with ARDS, 13 cm H_2O for patients without ARDS, and 14.5 cm H_2O for all patients collectively.

This study has notable strengths. This is among the few prospective studies exploring the link between ΔP and mortality in both pARDS and non-pARDS patients, with ΔP and other ventilatory parameters measured using hold maneuvers to minimize patient effort and provide detailed data.

However, there are limitations. First, only the initial 24-h ventilator settings were analyzed; subsequent ventilator pressure changes due to dynamic lung responses were not captured. Additionally, as a single-center study, the findings may be limited in generalizability.

Conclusion

In this single-center prospective observational study, driving pressure was significantly associated with an increased mortality risk in patients with pARDS and non-pARDS undergoing mechanical ventilation. Future randomized multicenter studies are needed to establish protocols targeting ΔP and determine optimal cut-off values.

Ethics

Ethics Committee Approval: This prospective, single-center observational study included patients admitted to the PICU.

The study protocol was approved by the University of Health Sciences Turkey, Dr. Behçet Uz Child Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee (decision no: 2020/07-02, date: 07.05.2020).

Informed Consent: Written informed consent was obtained from the parents/caregivers after the patient's initial clinical stabilization period.

Footnotes

Surgical and Medical Practices: G.A., S.T., Concept: E.S., U.K., H.A., Design: E.S., G.C., M.Ç., H.A., Data Collection and Process: G.A., S.T., Ö.S.S., Analysis or Interpretation: M.Ç., P.H., F.S., Literature Search: E.S., P.H., Ö.S.S., U.K., Writing: E.S., G.C., U.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Ferguson ND, Fan E, Camporota L, Antonelli M, Anzueto A, Beale R, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med. 2012;38:1573-82. Erratum in: Intensive Care Med. 2012;38:1731-2.
2. Santschi M, Jouvet P, Leclerc F, Gauvin F, Newth CJ, Carroll CL, et al. Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. Pediatr Crit Care Med. 2010;11:681-9.
3. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2015;16:428-39.
4. Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J, et al. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). Intensive Care Med. 2017;43:1764-80.
5. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301-8.
6. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med. 2013;369:2126-36.
7. Guo L, Xie J, Huang Y, Pan C, Yang Y, Qiu H, et al. Higher PEEP improves outcomes in ARDS patients with clinically objective positive oxygenation response to PEEP: a systematic review and meta-analysis. BMC Anesthesiol. 2018;18:172.
8. Khemani RG, Conti D, Alonzo TA, Bart RD 3rd, Newth CJ. Effect of tidal volume in children with acute hypoxemic respiratory failure. Intensive Care Med. 2009;35:1428-37.
9. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303:865-73.
10. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372:747-55.
11. Aoyama H, Pettenuzzo T, Aoyama K, Pinto R, Englesakis M, Fan E. Association of Driving Pressure with Mortality among Ventilated Patients with Acute Respiratory Distress Syndrome: a systematic review and meta-analysis. Crit Care Med. 2018;46:300-6.
12. Chen Z, Wei X, Liu G, Tai Q, Zheng D, Xie W, et al. Higher vs. Lower DP for Ventilated Patients with Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis. Emerg Med Int. 2019;2019:4654705.
13. Guérin C, Papazian L, Reignier J, Ayzac L, Loundou A, Forel JM; et al. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care. 2016;20:384.
14. Lanspa MJ, Peltan ID, Jacobs JR, Sorensen JS, Carpenter L, Ferraro JP, et al. Driving pressure is not associated with mortality in mechanically ventilated patients without ARDS. Crit Care. 2019;23:424.
15. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci Mde O, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308:1651-9.
16. Flori HR, Glidden DV, Rutherford GW, Matthay MA. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. Am J Respir Crit Care Med. 2005;171:995-1001.
17. Dahlem P, van Aalderen WMC, Hamaker ME, Dijkgraaf MGW, Bos AP. Incidence and short-term outcome of acute lung injury in mechanically ventilated children. Eur Respir J. 2003;22:980-5.
18. Schmidt MFS, Amaral A, Fan E, Rubenfeld GD. Driving pressure and hospital mortality in patients without ARDS: a cohort study. Chest. 2018;153:46-54.
19. Chiumello D, Carlesso E, Brioni M, Cressoni M. Airway driving pressure and lung stress in ARDS patients. Crit Care. 2016;20:276.
20. Raymondos K, Dirks T, Quintel M, Molitoris U, Ahrens J, Dieck T, et al. Outcome of acute respiratory distress syndrome in university and non-university hospitals in Germany. Crit Care. 2017;21:122.
21. Farias JA, Frutos F, Esteban A, Flores JC, Retta A, Baltodano A, et al. What is the daily practice of mechanical ventilation in pediatric intensive care units? A multicenter study. Intensive Care Med. 2004;30:918-25.
22. Randolph AG, Meert KL, O'Neil ME, Hanson JH, Luckett PM, Arnold JH, et al. The feasibility of conducting clinical trials in infants and children with acute respiratory failure. Am J Respir Crit Care Med. 2003;167:1334-40.
23. Henderson WR, Chen L, Amato MB, Brochard LJ. Fifty years of research in ARDS: respiratory mechanics in acute

respiratory distress syndrome. Am J Respir Crit Care Med. 2017;196:822-33.
24. Neto AS, Simonis FD, Barbas CS, Biehl M, Determann RM, Elmer J, et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: a systematic review and individual patient data analysis. Crit Care Med. 2015;43:2155-63.
25. Erickson S, Schibler A, Numa A, Nuthall G, Yung M, Pascoe E, et al. Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study. Pediatr Crit Care Med. 2007;8:317-23.
26. Zhu YF, Xu F, Lu XL, Wang Y, Chen JL, Chao JX, et al. Mortality and morbidity of acute hypoxemic respiratory failure and acute respiratory distress syndrome in infants and young children. Chin Med J. 2012;125:2265-71.
27. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA. 2016;315:788-800.
28. Laffey JG, Bellani G, Pham T, Fan E, Madotto F, Bajwa EK, et al. LUNG SAFE Investigators and the ESICM Trials Group: Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: The LUNG SAFE study. Intensive Care Med. 2016;42:1865-76.
29. Ceylan G, Topal S, Atakul G, Colak M, Soydan E, Sandal O, et al. Randomized crossover trial to compare driving pressures in a closed-loop and a conventional mechanical ventilation mode in pediatric patients. Pediatr Pulmonol. 2021;56:3035-43.

Turk J Intensive Care 2024;22:264-9
DOI: 10.4274/tybd.galenos.2023.77698

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Oğuzhan Kayhan,
Oktay Demirkıran

Workplace Violence Against Turkish Intensive Care Physicians: A Cross-sectional Study

Türk Yoğun Bakım Hekimlerine Karşı İş Yerinde Şiddet: Kesitsel Bir Çalışma

Received/Geliş Tarihi : 20.05.2023
Accepted/Kabul Tarihi : 08.11.2023

Oğuzhan Kayhan, Oktay Demirkıran
İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and Intensive Care, İstanbul, Turkey

Oğuzhan Kayhan MD (✉),
İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Anesthesiology and Intensive Care, İstanbul, Turkey

E-mail : oguzhankayhan@outlook.com
ORCID ID : orcid.org/0000-0001-5832-0080

***The abstract of this article was presented as an oral presentation at the 2022 Turkish Intensive Care Congress.**

ABSTRACT *Objective:* It was aimed to get the experience and opinions of intensive care physicians, who are health professionals who experience violence with increasing frequency.
Materials and Methods: The questionnaire, consisting of 28 multiple choice and open-ended questions, was answered by intensivists across the country.
Results: In the online questionnaire study, which was answered by 198 physicians, 44% male and 56% female, it was found that 86% of the physicians experienced violence in the hospital where they worked, and 47% were exposed to violence during their work in the intensive care unit. It was observed that the most common violence was verbal threats with and physical violence. Victims of violence stated that they mostly prefer to call hospital security (56%). It was determined that 65% of the violent incidents experienced were resolved by talking. The common view of the victims of violence and of the vast majority of all physicians was that the measures were insufficient and the violence would recur.
Conclusion: Violence in health is increasing all over the world and in Turkey. The precautions to be taken should be aimed at the patients and their relatives, as well as the health workers and the health system itself.
Keywords: Intensive care, violance, physician, workplace violance, violance in healthcare

ÖZ *Amaç:* Yer, zaman, kişi fark etmeksizin herkese yönelebilen şiddeti, giderek artan sıklıkta yaşayan sağlık çalışanlarından olan yoğun bakım hekimlerinin tecrübe ve görüşlerinin alınması amaçlandı.
Gereç ve Yöntem: Yirmi sekiz çoktan seçmeli ve açık uçlu sorudan oluşan anketin ülke çapında yoğun bakım hekimlerinin yanıtlaması sağlandı.
Bulgular: %44'ü erkek, %56'sı kadın olan 198 hekimin yanıtladığı online anket çalışmasında, hekimlerin %86'sının çalıştığı hastanede şiddet olayı yaşandığı, %47'sinin ise yoğun bakımda çalıştıkları süre boyunca şiddete maruz kaldıkları tespit edildi. Gerçekleşen şiddetin %62 oranıyla en fazla sözel tehdit olduğu, %30 oranında ise fiziksel şiddet olduğu görüldü. Şiddete uğrayanlar en fazla hastane güvenliğini aramayı (%56) tercih ettiğini belirtti. Yaşanan şiddet olaylarının %65'inin konuşarak çözüldüğü tespit edildi. Şiddete maruz kalanların ve tüm hekimlerin çok büyük çoğunluğunun ortak görüşünün tedbirlerin yetersizliği ve şiddet olaylarının tekrarlayacağı şeklindeydi.
Sonuç: Tüm dünyada ve ülkemizde sağlıkta şiddet artış göstermektedir. Alınması gereken önlemler hastalara ve yakınlarına yönelik olduğu gibi sağlık çalışanlarına ve sağlık sisteminin kendisine yönelik de olmalıdır.
Anahtar Kelimeler: Yoğun bakım, şiddet, hekim, iş yerinde şiddet, sağlıkta şiddet

Introduction

Workplace violence is a global problem. It was first defined in 1997 as "incidences in which individuals are abused, threatened or attacked in conditions related to their work, involving an explicit or implicit threat to their safety, well-being and health" (1).

In a year, violence in the health sector increases by up to 62% (2). The incidence of physical violence is 24%, and that of non-physical violence is 43% (2). In Turkey, this rate accounts for approximately half of all health workers (3).

In terms of all sectors, the frequency of violence in the health sector is at the top of the list (4).

Although it is the first possible inference that violence will decrease as countries' development level increases, the facts may be the opposite (5).

Violence in the workplace can take the form of physical and psychological attacks. It can take the form of assault, harassment, bullying, mobbing, abuse, sexual harassment, racial harassment, and threats. Because physical violence can be defined by everyone, awareness of this issue is high. However, there are many different types of psychological violence, and since awareness of this issue is gradually increasing, incidents of psychological violence are being noticed more and more.

Studies have found that among the risk factors defined for workplace violence, shift workers, younger workers, and those with long working hours per week are more likely to be exposed to any type of violence (2). In a large-scale systematic review, male workers, single workers, physicians, nurses, more experienced workers, and those of white ethnic origin were found to have a higher risk of exposure to violence (2).

The aim of this study was to investigate the history of exposure to violence and thoughts of physicians working in intensive care units.

Materials and Methods

The research, which was planned as a survey study, was conducted by answering an online questionnaire, which was created from 28 multiple choice and open-ended questions, by all intensive care physicians that could be reached across the country. The survey was prepared using Google Forms. The link to the survey was shared in WhatsApp and mail groups, including intensive care physicians from all over Turkey. The study was published on the home page of the Turkish Society of Intensive Care website for 1 week and for 1 month in the announcement section. The questionnaire was kept open for response for a period of 1 month and then closed for response.

Since the study was a survey of physicians, patients were not included in the study and therefore there was no need to obtain patient informed consent. The first 7 were questions inquiring about demographic data. The next 12 were about the physical conditions of the intensive care unit where the physician worked and the number of employees and patients. The last 8 consisted of questions about the characteristics and consequences of the violence.

The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (date: 19.09.2018, number: 72109855-604.01.01-60122).

Statistical Analysis

Chi-square analysis was used as the statistical method. The significance level was set as $p<0.05$. Independent variables, including demographic variables, are shown in frequency tables with numbers and percentages.

Results

Of the 224 intensive care physicians, 198 answered the questionnaire. Of the respondents, 44.4% (n=88) of the respondents were male and 55.6% (n=110) were female. Those who worked in the intensive care unit for 5 years or less were 37.4% (n=74), and those with 6 years or more were 62.6% (n=124). It was determined that the participants mainly worked in universities (41.9% n=83) and training and research hospitals (28% n=59) and mostly from anesthesiology and reanimation as their main branch (82.3% n=163).

It was determined that most of the physicians treated 6-10 patients (47% n=93), while nurses cared for 3 patients (57.1% n=113). According to the results of the study, the relatives of the patients did not participate in the treatment process, and the patient treatment information was mainly given by the intensive care physician every day of the week; it was determined that the nurses did not accompany the physicians while giving information.

85.9% (n=170) of the participants reported seeing violence in the hospital where they worked. The rate of those who were exposed to violence during their work in the intensive care unit was 47% (n=94).

The violence encountered in the intensive care unit was mostly verbal threats [61.7% (n=58)]. It was stated that 41.5% (n=39) experienced verbal attack, 29.8% (n=28) physical violence, and 6.4% (n=6) non-verbal threat (Figure 1). It was observed that violence was mainly applied by relatives of patients (47%).

The reactions of the participants who faced violence are; 8.5% (n=8) called the police, 29.8% (n=28) gave white code, 9.6% (n=9) responded to violence with violence, 56.4% (n=53) called the hospital security, 46.8% (n=44) tried to reach an agreement by talking and 4 participants stated that they did not give any reaction to violence (Figure 2).

It was reported that 65% of the violence cases were resolved by talking, 11.7% complained to the police, 14.9% were prosecuted, and 2.1% were sentenced to prison.

While 97% of those who were exposed to violence thought that efforts to prevent violence in the field of health were insufficient, this rate was 96% among all participants. Among those who were exposed to violence, 84% thought that violence would be repeated was 84%.

Chi-square analysis in independent groups was conducted to determine whether there was a significant relationship between violence and the independent variables asked in the questionnaire. A significant correlation was found only between the type of hospital and the frequency of violence (p=0.009).

Among the respondents, 47% of men and 48% of women were exposed to violence. Although 37% of the men were exposed to violence, 25% were found to have been subjected to physical violence (Figure 3).

Considering the number of intensive care patients, 59% of physicians who treated >10 patients were exposed to violence, whereas 44% of physicians who treated 10 patients experienced violence (Figure 4). While the rate of violence against physicians in intensive care units where a nurse cares for 3 or more patients was 48%, it was 47% for those under 3 (Figure 4).

At the top of the measures demanded to be taken to prevent violence was the enactment of laws specific to violence in the field of health (Table 1).

Discussion

It is understood from the data obtained in this study that most physicians working in intensive care units are exposed to any type of violence. Almost all of them believe that the measures taken against violence are insufficient. The vast majority demand preventive laws, deterrent penalties, and education programs.

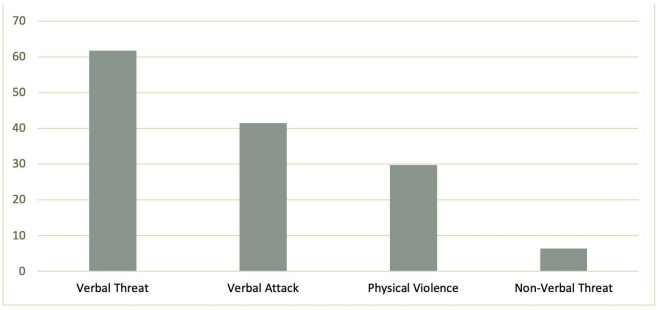

Figure 1. Types of violence exposure of intensive care physicians (%)

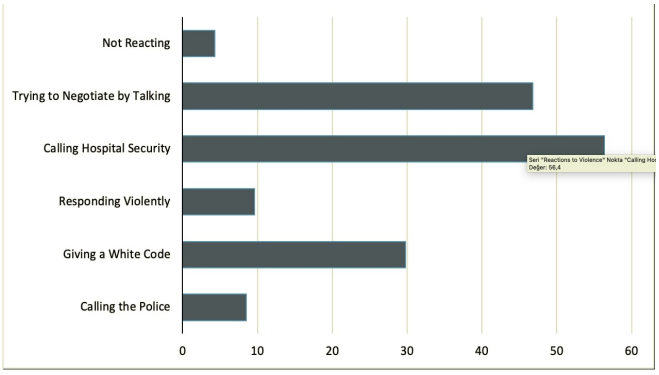

Figure 2. Reactions to violence (%)

Figure 3. Frequency of physical violence by gender (%)

Table 1. What measures do you think should be taken to prevent violence in healthcare? [% (n)]	
Enacting laws specific to violence in health	76% (151)
Increasing prison sentences	68% (134)
Subjecting attackers to compulsory education programs	57% (113)
Increasing fines	55% (108)
Prevention of receiving services from the health institution where the violence took place	52% (102)
Prohibition of benefiting from the Social Security Institution for a period of time	35% (69)
Prohibition of benefiting from the Social Security Institution indefinitely	30% (59)

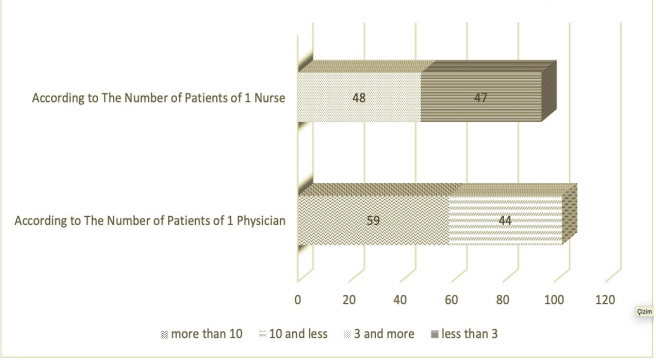

Figure 4. Frequency of violence by the number of patients cared for by physicians and nurses (%)

Studies have revealed that violence against healthcare professionals is experienced at varying rates but at high frequencies in all countries worldwide. In a meta-analysis in which 65 studies of 61,800 health workers from 30 countries were evaluated and physical violence was investigated, it was reported that the 1-year frequency of violence was 19% (5). It has been concluded that the rate of violence is 26% in Europe, 24% in the United States, and 21% in Africa, and the frequency of violence increases as the income levels of the countries increase. The highest frequency was observed in nursing homes 30%, followed by tertiary healthcare institutions. It was reported that 1-year violence events were 23% against nurses and 15% against physicians, and the difference was statistically significant. The frequency of violence was found to be higher in urban areas (26%) than in rural areas (6%). What we would probably predict is less violence in health in countries with better socioeconomic status. This meta-analysis, on the other hand, says the opposite. If we assume that the level of development is an indicator of civilization, we can also assume that civilized countries should have fewer violent people, but unfortunately we cannot see this in real life.

After the violence, it is important what attitude the country adopts in accordance with the policies developed against it. It is necessary for health workers to feel safe that the state's attitude toward violence is clearly revealed by the administrators. A cross-sectional study conducted in Bangladesh reported that 43% of health workers were exposed to any form of violence, and 16% of them experienced physical violence (6). 65% of the victims of violence reported that nothing was done against the violence they experienced, and 44% of the cases in which something was done for violence were inconclusive. In a study conducted among physicians in Italy, the frequency of verbal violence in the last 1 year was reported to be 52% and the frequency of physical violence was 4% (7). 61% of those who were exposed to verbal violence and 22% of those who were exposed to physical violence stated that they did not have any reaction. In our study, it was seen that the prevailing opinion was that the measures taken were very insufficient (96%) and that the perpetrator would use violence again (84%). The high demands of physicians, such as new laws, high penalties, and compulsory education programs, are due to their insecurity in the current situation.

Beyond the acute consequences of violence, victims also experience psychological consequences experienced by the victims. They can be affected in different ways, from depression to post-traumatic stress disorder. A study conducted with family health center workers in Brazil reported that 36% of the victims of violence showed signs of depression and 16% probably had major depression (8). It was stated that as the violence experienced by the victims increased, their depressive symptoms also increased. It would not be wrong to think that a similar situation exists in our country. The quality of life of health workers, who are forced to live under harsh conditions, also decreases as a result of the psychological state of exposure to violence. Job satisfaction decreases, and the desire for job change becomes widespread. The satisfaction of patients, who have to receive service from unhappy and restless health workers, from the health system, which can only be performed with the devotion of employees, is gradually decreasing. Because the doctor he/she went to did not pay as much attention to the patient as he/she wanted due to his/her workload and possible depression, he/she goes to another doctor, then to another doctor, and the health system is thus overwhelmed. This results in increased violence because healthcare workers are overwhelmed by the workload due to busier hospitals and patients who require more attention and time.

The most undesirable and traumatic outcome of violence is the killing of healthcare workers. A study conducted in the United States reported that 61 healthcare workers died due to workplace violence between 2003 and 2016, of which 52% were due to suicide and 34% to murder (9). It has been reported that 28% of the victims were doctors, 21% were nurses, and the rest were other health and safety workers. Regardless of the circumstances, death can affect survivors in a wide variety of ways. The death of a physician as a result of murder not only deeply hurts his/her relatives but also

deeply affects all physicians as a professional group. Every physician experiences this trauma within himself/herself, and his/her love and commitment to his/her profession is damaged. Physicians, who are the owners of a profession with high self-sacrifice, come to the point of questioning their own self-sacrifice, lives, and professions as a result of every physician murder, and this even goes to the point of changing professions. Considering the effort and years spent training a physician, the loss is.

In a study conducted in China, 459 files were opened due to violence against healthcare professionals as a result of the scanning of judicial system records between 2013 and 2016 (10). It has been reported that the highest risk rate is in primary healthcare institutions (43%), the most risky department is emergency (51%), physicians are the most risky group (55%, and the most common type of violence is physical 77%). In 1.6% of the cases, the event resulted in death. In our research, the results of violent incidents were questioned, and only 15% of them were brought to the judiciary. Every unpunished crime has a chance of being repeated. The reliability of law is one of the most important elements of a country. A healthcare worker who has been subjected to violence has no other choice but to apply to the judiciary. The state and judicial system will protect the physician.

Unfortunately, the situation in our country- where medicine is the most valued profession- is not different from the rest of the world. In a study conducted in Turkey, 447 healthcare workers were surveyed (11). 37% of the respondents, 37% reported having experienced physical violence during their working life, and 89% had been verbally abused. It was reported that physical violence occurred in 41% of the patients, in 34% of the patients, in midwives, nurses, and emergency medical technicians who answered the questionnaire, and verbal abuse rates were 95% and 85%. It was stated that 62% of physical violence and 86% of verbal abuse incidents were not investigated as crimes. Furthermore, 71% of physical violence incidents and 83% of verbal abuse incidents stated that they did not report the incident because they did not believe that it would be beneficial. Similar results were obtained in our study, and it is understood that the belief of the employees in Turkey that the law will adequately protect them against violence is quite weak.

Studies conducted all over the world have reported that emergency services are the most risky area for violence (2). A survey was conducted with emergency service workers in Turkey, and their exposure to workplace violence in the last 5 years was questioned (12). Of the 124 employees who answered the questionnaire, 87% reported that they had been exposed to aggressive behavior in the last 5 years. 97% of the responding physicians and 82% of the nurses and midwives, 97% stated that they were exposed to aggressive behavior. Furthermore, 16% of the participants stated that they have been subjected to physical violence, and 23% have witnessed physical violence. While 43% of those who were exposed to violence survived the event without trauma, 38% reported that they experienced psychological trauma, and 4% reported that they were life-threatening. Intensive care units are similar to emergency care units in terms of patient vital risks. However, the risk of violence may be lower because intensive care units are more closed than emergency services, and relatives of patients have much more limited access. In addition, although the severity of the patients' condition is mostly accepted by their relatives, the possibility of reactive violence increases when the patient's relatives lose their patient before this period of acceptance.

Conclusion

As a result, intensive care physicians in Turkey are exposed to high rates of violence and believe that the measures taken are inadequate.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (date: 19.09.2018, number: 72109855-604.01.01-60122).

Informed Consent: Since the study was a survey of physicians, patients were not included in the study and therefore there was no need to obtain patient informed consent.

Footnotes

Authorship Contributions

Concept: O.K., O.D., Design: O.K., O.D., Data Collection or Processing: O.K., O.D., Analysis or Interpretation: O.K., O.D., Literature Search: O.K., O.D., Writing: O.K., O.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Wynne R, Clarkin N, Cox T, Griffith A. Guidance on the prevention of violence at work: Office for Official Publications of the European Communities; 1997.
2. Liu J, Gan Y, Jiang H, Li L, Dwyer R, Lu K, et al. Prevalence of workplace violence against healthcare workers: a systematic review and meta-analysis. Occup Environ Med. 2019;76:927-37.
3. Pinar T, Acikel C, Pinar G, Karabulut E, Saygun M, Bariskin E, et al. Workplace Violence in the Health Sector in Turkey: A National Study. J Interpers Violence. 2017;32:2345-65.
4. Nelson R. Tackling violence against health-care workers. Lancet. 2014;383:1373-4.
5. Li YL, Li RQ, Qiu D, Xiao SY. Prevalence of Workplace Physical Violence against Health Care Professionals by Patients and Visitors: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2020;17.
6. Shahjalal M, Gow J, Alam MM, Ahmed T, Chakma SK, Mohsin FM, et al. Workplace Violence Among Health Care Professionals in Public and Private Health Facilities in Bangladesh. Int J Public Health. 2021;66:1604396.
7. Firenze A, Santangelo OE, Gianfredi V, Alagna E, Cedrone F, Provenzano S, et al. Violence on doctors. An observational study in Northern Italy. Med Lav. 2020;111:46-53.
8. da Silva AT, Peres MF, Lopes Cde S, Schraiber LB, Susser E, Menezes PR. Violence at work and depressive symptoms in primary health care teams: a cross-sectional study in Brazil. Soc Psychiatry Psychiatr Epidemiol. 2015;50:1347-55.
9. Braun BI, Hafiz H, Singh S, Khan MM. Health Care Worker Violent Deaths in the Workplace: A Summary of Cases From the National Violent Death Reporting System. Workplace Health Saf. 2021;69:435-41.
10. Cai R, Tang J, Deng C, Lv G, Xu X, Sylvia S, et al. Violence against health care workers in China, 2013-2016: evidence from the national judgment documents. Hum Resour Health. 2019;17:103.
11. Hamzaoglu N, Türk B. Prevalence of Physical and Verbal Violence Against Health Care Workers in Turkey. Int J Health Serv. 2019;49:844-61.
12. Erkol H, Gökdoğan MR, Erkol Z, Boz B. Aggression and violence towards health care providers--a problem in Turkey? J Forensic Leg Med. 2007;14:423-8.

Turk J Intensive Care 2024;22:270-80
DOI: 10.4274/tybd.galenos.2023.58815

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Özhan Özcan,
İlkin Çankayalı,
Ajda Turhan,
Mehmet Sezai Taşbakan,
Hüseyin Aytaç Erdem
Pervin Korkmaz,
Kubilay Demirağ,
Mehmet Uyar,
Tansu Yamazhan,
Yeşim Aydınok

Evaluation of the Effectiveness of Convalescent Plasma Therapy in Severe and Critical COVID-19

Şiddetli ve Kritik COVID-19 Hastalarında Konvelesan Plazma Tedavisinin Etkinliğinin Değerlendirilmesi

Received/Geliş Tarihi : 09.07.2023
Accepted/Kabul Tarihi : 29.11.2023

Özhan Özcan, İlkin Çankayalı, Kubilay Demirağ, Mehmet Uyar
Ege University Faculty of Medicine, Department of Anesthesiology, Division of Critical Care, İzmir, Turkey

Ajda Turhan
Blood Bank, Ege University Faculty of Medicine, İzmir, Turkey

Mehmet Sezai Taşbakan, Pervin Korkmaz
Ege University Faculty of Medicine, Department of Chest Diseases, İzmir, Turkey

Hüseyin Aytaç Erdem, Tansu Yamazhan
Ege University Faculty of Medicine, Department of Infectious Diseases, İzmir, Turkey

Yeşim Aydınok
Ege University Faculty of Medicine, Department of Pediatric Hematology and Oncology, İzmir, Turkey

Özhan Özcan MD (✉),
Ege University Faculty of Medicine, Department of Anesthesiology, Division of Critical Care, İzmir, Turkey

E-mail : ozhanturkey@hotmail.com
ORCID ID : orcid.org/0000-0001-9928-2383

ABSTRACT *Objective:* Relevant studies have suggested that the administration of convalescent plasma (CP) collected from coronavirus disease-2019 (COVID-19) patients who have recovered from the infection and whose plasma contains antibodies against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is safe and may be effective in treating COVID-19 patients. The present study aimed to investigate whether the number of CP doses administered, the power of the immunoglobulin (Ig)G ratio and the time of CP administration following positive SARS-CoV-2 polymerase chain reaction (PCR) had an impact on the 30-day in-hospital mortality.

Materials and Methods: This single-center retrospective study was conducted with patients who were hospitalized and met the severe/critical COVID-19 disease criteria and received CP. Demographics, comorbidities, co-medications, onset of symptoms, duration between SARS-CoV-2 PCR testing and hospitalization, the time of the first CP administration, laboratory results, respiratory support needs, O_2 saturation, fever at the baseline, acute physiologic, chronic health evaluation (APACHE) II scores and SOFA scores were recorded.

Results: Of the 224 patients with the mean age of 64.2±14.5 (19-91) years, 143 were male. The most common comorbidities were hypertension and congestive heart failure. Chronic renal failure, mechanical ventilation needs, PO_2/FiO_2 <300, clinically rapid progression, persistent fever, sequential organ failure assessment score increase and increased vasopressor need were associated with increased mortality. There was a statistically significant difference between the deceased (14.0±8.2) and survivor (8.74±5.28) groups in terms of APACHE II scores (p<0.001). The number of CP units administered, the power of the IgG ratio in the CP units and the timing of CP administration had no effect on the need for respiratory support and mortality rate. CP-associated complications were observed in 11 (0.5%) patients.

Conclusion: In conclusion, CP therapy was not associated with improved survival or other positive clinical outcomes in severe/critical COVID-19 patients.

Keywords: Severe/critical COVID-19, intensive care unit, convalescent plasma, the power of the IgG ratio, SOFA score, the APACHE II score, macrophage activation syndrome

ÖZ *Amaç:* İlgili çalışmalarda, iyileşen ve plazmaları şiddetli akut solunum yolu sendromu-koronavirüs-2'ye (SARS-CoV-2) karşı antikorlar içeren koronavirüs hastalığı-2019 (COVID-19) hastalarından toplanan konvelesan plazma (KP) uygulanmasının güvenli olduğunu ve COVID-19 hastalarının tedavisinde etkili olabileceğini öne sürülmekte. Bu çalışma, pozitif SARS-CoV-2 polimeraz zincir reaksiyonu (PZR) takiben uygulanan KP dozlarının sayısının, immünoglobulin (Ig)G oranının gücünün ve KP uygulama süresinin 30 günlük hastane içi mortalite üzerinde bir etkisi olup olmadığını araştırmayı amaçladı.

Gereç ve Yöntem: Bu tek merkezli retrospektif çalışma, hastaneye yatırılan ve ciddi/kritik COVID-19 hastalığı kriterlerini karşılayan ve KP alan hastalarla yapılmıştır. Demografi, komorbiditeler, ek ilaçlar, semptomların başlangıcı, SARS-CoV-2 PZR testi ile hastaneye yatış arasındaki süre, ilk KP uygulamasının zamanı, laboratuvar sonuçları, solunum desteği ihtiyaçları, O_2 satürasyonu, başlangıçtaki ateş, akut fizyolojik, kronik sağlık değerlendirmesi (APACHE) II skorları ve ardışık organ yetmezliği değerlendirmesi skorları kaydedildi.

Bulgular: Yaş ortalaması 64,2±14,5 (19-91) olan 224 hastanın 143'ü erkekti. En yaygın komorbiditeler hipertansiyon ve konjestif kalp yetmezliği idi. Kronik böbrek yetmezliği, mekanik ventilasyon ihtiyacı, PO_2/FiO_2 <300, klinik olarak hızlı ilerleme, inatçı ateş, SOFA skorunda artış ve artmış vazopresör ihtiyacı mortalite artışı ile ilişkilendirildi. APACHE II puanları açısından ölen (14,0±8,2) ve yaşayan (8,74±5,28) grupları arasında istatistiksel olarak anlamlı fark vardı (p<0,001). Uygulanan KP ünitesi sayısı, KP ünitelerindeki IgG oranının gücü ve KP uygulama zamanlaması, solunum desteği ihtiyacı ve ölüm oranı üzerinde hiçbir etkiye sahip değildi. 11 (%0,5) hastada KP ile ilişkili komplikasyonlar görüldü.
Sonuç: Sonuç olarak, KP tedavisi, şiddetli/kritik COVID-19 hastalarında sağkalım veya diğer pozitif klinik sonuçlarla ilişkili değildi.
Anahtar Kelimeler: Şiddetli/kritik COVID-19, yoğun bakım ünitesi, konvelesan plazma, IgG oranının gücü, SOFA skor, APACHE II skoru, makrofaj aktivasyon sendromu

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection presents with a wide range of clinical symptoms, ranging from asymptomatic to severe pneumonia, multiple organ failure, and death (1-3). Although 80% of reported cases are estimated to have a mild or asymptomatic course of infection, approximately 5% are admitted to the intensive care unit (ICU) with acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, or all three (4-6). Patients with a respiratory rate >30/min or SpO_2 in room air <90%, along with clinical signs of pneumonia, have been defined as severe coronavirus disease-2019 (COVID-19) cases, whereas those who have ARDS or respiratory failure requiring ventilation, sepsis, or septic shock are considered critical COVID-19 cases (7).

In the absence of other specific therapies, convalescent plasma (CP) has been used as either a preventive or therapeutic agent to provide immediate passive immunity, with variable success in various infectious diseases (8-10). In the early period of the COVID-19 pandemic, randomized controlled studies and case series have suggested that the administration of CP was collected from patients with COVID-19 who recovered from the infection and whose plasma contains antibodies against SARS-CoV-2, which is safe and may be effective in treating patients with COVID-19 (11-14). Concurrent with these studies, in August 2020, the American Food and Drug Administration (FDA) issued an Emergency Use Authorization for CP for the treatment of hospitalized patients with COVID-19 (15).

Our study aimed to evaluate the use of COVID-19 CP in patients with severe and critically hospitalized COVID-19 who lacked information regarding hospital mortality and changes in clinical and laboratory markers in the early course of the disease.

Materials and Methods

Patients

This single-center retrospective study was conducted at Ege University Hospital after receiving approval from the Clinical Research Ethics Committee (number: 20-5T/48).

Adult patients admitted to the COVID-19 ICU and services dedicated to treating patients with COVID-19 who met the severe/critical disease criteria and received COVID-19 CP between April 2020 and January 2021 were included in the study.

Study Protocol and Data Collection

CP collection and administration were performed according to the COVID-19 Immune (Convalescent) Plasma Supply and Clinical Use Guidelines of the Ministry of Health of Turkey (16).

Clinical and specific laboratory data were obtained from the electronic file records of the patients. The demographics, comorbidities, co-medications, onset of symptoms, time lag between SARS-CoV-2 polymerase chain reaction (PCR) testing and hospitalization, and time of first CP use were recorded. Laboratory assessments associated with the severity of COVID-19, including neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin, ferritin, D-dimer, and platelet values, were performed. Respiratory support needed, O_2 saturation, fever, and relevant laboratory parameters were determined at baseline, 48 and 72 hours, and 5 days after CP administration. Acute physiologic, chronic health evaluation II scores were obtained during hospitalization, and sequential organ failure assessment scores were recorded during hospitalization, baseline, and 5 days after CP administration. Immunoglobulin (Ig)A deficiency was excluded in all patients before CP transfusion. Adverse events occurred within the first 24 hours after CP infusion were noted.

All patients were transfused with one unit of COVID-19 CP. The 2nd and 3rd units of CP, at least 24 hours apart, were transfused based on the physician's judgment of worsening the patients' respiratory, hemodynamic, and laboratory parameters due to COVID-19.

The patients received corticosteroids, antiviral agents, anticytokines, and antiplatelet/anticoagulants by considering the current treatment protocols for COVID-19 (17-24) within the scope of the recommended basic treatments specific to the patient.

Production and Storage Conditions of COVID-19 CP

All plasma donors had confirmed COVID-19 by SARS-CoV-2 PCR test positivity and were donated at least 14 days after complete resolution of COVID-19 symptoms and negative PCR testing, or 28 days after well-being. Donors were approximately 18-55 years, and all provided written informed consent at the time of plasmapheresis. All donors met the standard blood donor criteria and were documented to be negative for hepatitis B, hepatitis C, HIV, and syphilis, per standards in Turkish regulations, and exhibited strong IgG positivity in the immunochromatographic fast test for IgM and IgG.

A total of 200-600 cc plasma was collected using the apheresis method using the Trima Accel® Automated Blood Collection System (Terumo BCT) and divided into two or three bags of 200 mL each. CPs to be used in the first six hours were kept unfrozen, while the others were stored frozen. Those used as liquid plasma in the first six hours of the collection were subjected to 25 Gy Gamma irradiation.

Following the donation, all donor serum samples were tested with Euroimmune SARS-CoV-2 IgG ELISA (Euroimmun, Lübeck, Germany) to detect SARS-CoV-2 spike protein subunit 1 (S1). The results were expressed as the ratio of the optical density of the sample to that of the internal calibrator supplied with the kit. The threshold value for positive results was ≥1.1, and values between 0.8 and 1.0 were considered borderline positive.

We evaluated whether the number of CP doses administered (i.e., 1-3 units), power of the IgG ratio [i.e., low (1.1-2.0), moderate (2.1-4.0), and high (>4.1)], or the time of CP administration following positive SARS-CoV-2 PCR [i.e., very early (0-3 days), early (4-7 days), and late (>7 days)] had an impact on 30-day in-hospital mortality.

Statistical Analysis

The statistical analyses were performed using IBM SPSS Statistics 26 software (IBM Corp., Armonk, NY). Continuous variables with normal and non-normal distributions were summarized as mean ± standard deviation (SD) and median, respectively. Categorical variables are expressed as frequencies or percentages. Differences between the living and deceased groups were analyzed using the chi-square test. Mann-Whitney U test was used for continuous independent variables and the Wilcoxon signed-rank test for continuous dependent variables (in which the values were evaluated relative to the baseline value).

A One-Way ANOVA test was used for the independent evaluation of dependent variables in the CP subgroup analyses. The post hoc test (Tukey) was used to determine differences between the CP subgroups during follow-up.

All analyses were performed using the 95% confidence interval, and significance was assessed at the $p<0.05$ level.

Results

CP donations were made from the donors between 24 and 188 days (median: 80 days, SD: ±44.5 days) after the onset of their first symptoms. A total of 417 CP doses were used in 224 patients. Out of these 417 doses, 407 (97.6%) were IgG-positive, and strong positivity (IgG ratio >4) was detected in 58.3% of those.

When CP treatment was commenced, 173 of 224 patients (77%) were in the ICU. The demographic information and admission characteristics of the patients are presented in Table 1. The mean age of the patients was 64.219-91) 14.5±) years, and 143 were males. The most common comorbidities were hypertension (HT) and congestive heart failure (CHF), whereas the presence of chronic renal failure (CRF) was found to be associated with increased mortality. MV needs, PO_2/FiO_2 <300, clinically rapid progression, persistent fever, SOFA score increase of >2, and increased vasopressor need were detected to be linked to increased mortality. The mean CP administration time after positive SARS-CoV-2 PCR was 5.893.95± days, and after hospitalization was 4.093.39± days. Overall, the mean durations of stay in the ICU was 10.958.5± days, and in the hospital, 17.639.2± days. The APACHE score was 14.08.2± in the deceased group and 8.745.28± in the survivor group, and the difference was statistically significant

Table 1. Demographic information and clinical data of the patients receiving CP					
		Survivor group (n=123)	**Deceased group (n=101)**	**Total (n=224)**	**p-value**
Age (mean ± SD) (years)		60.85±14.796	68.31±13.029	64.21±14.5	< 0.001
Gender	Female	48 (59.3)	33 (40.7)	81 (36.2)	0.325
	Male	75 (52.4)	68 (47.6)	143 (63.8)	
Comorbidity (%)	Hypertension/congestive heart failure	58 (50)	58 (50)	116	0.126
	Diabetes mellitus	39 (52)	36 (48)	75	0.535
	Coronary artery disease	11 (39.3)	17 (60.7)	28	0.076
	Chronic renal failure	10 (32.3)	21 (67.7)	31	0.006
	Chronic obstructive pulmonary disease	9 (52.9)	8 (47.1)	17	0.865
	Malignancy	7 (41.2)	10 (58.8)	17	0.236
	Hyperlipidemia	2 (50)	2 (50)	4	1.000
CP Indications (%)	Invasive mechanical ventilator need	28 (22.8)	77 (76.2)	105	<0.001
	PaO_2/FiO_2 <300	35 (28.5)	59 (58.4)	94	<0.001
	SpO_2 sat <90	44 (35.8)	38 (37.6)	82	0.775
	Respiratory rate >30/min	38 (30.9)	43 (42.6)	81	0.070
	PaO_2 <70 mm Hg	38 (30.9)	28 (27.7)	66	0.604
	Rapid progression	21 (17.1)	30 (29.7)	51	0.025
	Persistent fever	32 (26.0)	15 (14.9)	47	0.041
	SOFA score increase >2	5 (4.1)	41 (40.6)	46	<0.001
	Increased CT infiltration	22 (17.9)	13 (12.9)	36	0.304
	Vasopressor need	1 (0.8)	18 (17.8)	19	<0.001
CP time (day) (mean ± SD)	After PCR positivity	6.00±3.737	5.76±4.203	5.89±3.947	0.43
	After hospitalization	3.93±3.147	4.30±3.66	4.09±3.386	0.93
APACHEII (mean ± SD)		n=72 8.74±5.28 (1-24)	n=93 14.0±8.19 (2-39)	n=165 11.70±7.52 (1-39)	<0.001
SOFA (mean ± SD)	Hospitalization day	n=73 3.25±1.89 (0-9)	n=91 4.59±2.59 (1-14)	n=164 3.99 (0-14)	<0.001
	CP baseline	n=73 3.49±1.90 (0-9)	n=92 6.14±2.64 (1-14)	n=165 4.97 (0-14)	<0.001
	Day 5	n=73 2.86±1.96 (0-8)	n=70 6.66±2.60 (0-14)	n=143 4.76 (0-14)	<0.001
Respiratory support (at the first CP) (%)	MV/NIV/HFNC*	37 (32.4)	77 (67.5)	114	<0.001
	Mask and nasal O_2/room air	86 (78.1)	24 (21.8)	110	<0.001
Stay duration (day) (mean ± SD)	Intensive care unit (mean)	8.27±8.7	14.17±7.02	10.95±8.5	<0.001
	Hospital (mean)	17.93±9.06	17.26±8.82	17.63±9.2	0.686

* MV: Mechanical ventilator, NIV: non-invasive mechanical ventilator, HFNC: high flow nasal cannula, SOFA: the sequential organ failure assessment score, SD: standard deviation, CP: convalescent plasma

Table 2. Survival analysis of laboratory parameters related to COVID-19 severity				
		Survivor group (n=123) (mean ± SD)	**Deceased group (n=101) (mean ± SD)**	**p*-value**
CRP (0-5 mg/L)	Baseline	88.2±67.7	119.7±95.1	0.015
	48h	58.1±52.5	95.1±79.4	
	72h	45.6±52.4	98.7±72.2	
	D5	28.5±34.1	78.6±50.4	
Procalcitonin (<0.05 µg/L)	Baseline	1.47±2.0	2.41±3.9	<0.001
	48h	0.52±0.54	1.47±2.1	
	72h	0.60±0.64 p$^{\gamma}$=0.043	1.40±1.6	
	D5	0.28±0.26	1.54±2.5	
D-dimer (<550 µg/L FEU)	Baseline	1504.8±1312.6	2592.0±1613.5	p<0.001
	48h	2016.7±1557.7 p$^{\gamma}$=0.011	2971.6±1567.2 p$^{\gamma}$=0.001	
	72h	1818.2±1551.3	3313.6±1433.6 p$^{\gamma}$=0.002	
	D5	1824.8±1480.4	3547.0±1432.0 p$^{\gamma}$=0.001	
Ferritin (30-400 µg/L)	Baseline	913.8±1143.3	2119.6±6052.3	p=0.004
	48h	941.2±1138.5	1409.1±1526.5	
	72h	969.2±1048.4	1463.5±3182.5	
	D5	753.7±761.3	2645.0±8799.2	
NLR	Baseline	10.6±14.1	18.1±13.4	p<0.001
	48h	10.3±11.1	19.6±14.1 p$^{\gamma}$=0.019	
	72h	9.2±6.3	22.9±23.4 p$^{\gamma}$=0.006	
	D5	8.55±6.0 p$^{\gamma}$=0.030	25.2±24.2 p$^{\gamma}$<0.001	
Platelet count (150-450 10^3/µL)	Baseline	274.2±104.7	252.2±126.5	p=0.041
	48h	298.2±108.7 p$^{\gamma}$<0.001	237.7±130.4	
	72h	323.2±111.6 p$^{\gamma}$<0.001	243.6±129.1	
	D5	342.5±112.8 p$^{\gamma}$<0.001	242.9±140.3	

p*: Intergroup variation in the baseline values, p$^{\gamma}$: variation in the follow-up results relative to the baseline value, CRP: C-reactive protein, NLR: neutrophil to lymphocyte ratio, COVID-19: coronavirus disease-2019, SD: standard deviation

(p<0.001). The SOFA scores were statistically higher on the day of hospitalization and on the first and the 5th day of CP administration in the deceased group (p<0.001) (Table 1).

The macrophage activation syndrome (MAS)-like inflammation indicators, including baseline CRP, procalcitonin, D-dimer, ferritin, and NLR values, were significantly higher in the deceased group than in the survivor group. Comparing the baseline values, significant increases in the D-dimer and NLR values in the deceased group and the platelet count in the survivor group were observed during the sequential follow-up (Table 2). Although there was no significant difference between the baseline levels of the inflammation indicators between the groups that received low, moderate, and high IgG ratios in CPs, except for the platelet value change in high IgG ratios, no consistent changes were observed on those parameters during follow-up between the groups. It was statistically significant that the platelet value increased relative to the basal value during sequential follow-up in the group with a high Euroimmun IgG ratio (Table 3).

The number of CP units, power of the IgG ratio in the CP units, and timing of CP administration did not impact the need for respiratory support and mortality rate (Table 4). The SOFA score did not significantly differ between the groups receiving different power of IgG ratio (Table 5)

CP-associated adverse events were observed in 11 (0.5%) patients; the most common complication was fever in eight patients. In addition, two patients had transfusion-related acute lung injury (TRALI) and one patient had transfusion-

Table 3. Evaluation of laboratory parameters related to COVID-19 severity and MAS based on the Euroimmun IgG ratio in the first administered CP

		Low IgG ratio 1.1-2.0 (mean ± SD)	Moderate IgG ratio 2.1-4.0 (mean ± SD)	High IgG ratio >4.1 (mean ± SD)	p*-value
CRP (0-5 mg/L)	Baseline	91.8±73.3	103.1±84.4	105.5±85.4	0.846
	48h	63.7±53.2	84.2±57.8	75.2±68.4	0.239
	72h	63.8±88.9	73.4±61.8	70.6±80.7	0.276
	D5	35.6±61.8	66.9±65.8	46.6±59.3	0.015
	p$^{\gamma}$	<0.001	0.140	<0.001	
D-dimer (<550 µg/L FEU)	Baseline	1998.7±1480.2	2235.4±1636.8	1907.4±1523.1	0.499
	48h	2398.7±1620.8	2733.2±1696.6	2323.6±1610.5	0.382
	72h	2085.9±1644.2	2574.1±1795.4	2382.9±1643.2	0.620
	D5	2055.2±1697.9	2671.9±1695.6	2498.2±1690.9	0.364
	p$^{\gamma}$	0.410	0.007	0.252	
Ferritin (30-400 µg/L)	Baseline	3271.9±10982.0	1365.1±2420.7	1120.5±1260.0	0.569
	48h	993.6±1139.0	1405.6±2019.1	1113.9±1173.8	0.958
	72h	1887.9±4930.2	647.5±734.8	1106.3±1008.8	0.061
	D5	699.3±675.5	813.9±828.2	1829.3±6727.1	0.182
	p$^{\gamma}$	0.228	0.960	0.638	
NLR	Baseline	16.7±15.8	15.3±13.3	13.3±13.9	0.295
	48h	16.1±14.2	18.0±18.1	12.6±10.3	0.135
	72h	15.1±13.1	21.3±32.4	12.9±10.3	0.327
	D5	13.6±12.4	20.2±28.3	14.3±14.9	0.457
	p$^{\gamma}$	0.465	0.544	0.205	
Platelet count (150-450 10^3/µL)	Baseline	281.2±113.9	276.0±131.9	256.0±110.7	0.229
	48h	286.5±134.7	280.1±154.3	264.4±107.2	0.631
	72h	309.0±127.0	301.6±147.2	276.5±119.1	0.405
	D5	319.3±130.2	316.3±148.9	299.5±129.6	0.621
	p$^{\gamma}$	0.670	0.383	<0.001	

p*: Intergroup variation, p$^{\gamma}$: variation in follow-up results, CP: convalescent plasma, SD: standard deviation, COVID-19: coronavirus disease-2019, NLR: neutrophil to lymphocyte ratio, Ig: immunoglobulin, MAS: macrophage activation syndrome, CRP: C-reactive protein

associated circulatory overload (TACO); no mortality caused by complications was determined (Table 6).

Discussion

CP serum and immunoglobulin is a passive immunization method that has been used for approximately 100 years to prevent and treat outbreaks in which no vaccine or pharmacological intervention is available. The first CP administration was reported during the pandemic period of Spanish influenza A (H1N1) pneumonia (1918-1920); the meta-analysis of studies conducted during this pandemic revealed that CP reduces mortality (25). In recent years, CP has been used for Middle East respiratory syndrome, SARS caused by SARS-coronavirus-1 and Ebola (26,27).

However, in many large-scale randomized controlled clinical trials, the results indicated that CP treatment does not contribute to disease progression or to mortality in patients with COVID-19 (28-32). Further, in May 2021, it was reported in the Cochrane Review that there is a high degree of certainty in the evidence that CP for the treatment of individuals with moderate to severe COVID-19 does not reduce mortality and has little or no effect on measurements of clinical improvement (33). On the other

Table 4. Age, gender, respiratory support need and 30-day in-hospital mortality assessment in the groups

	CP doses administered (unit)				Power of the EI IgG ELISA				The time of CP administration following PCR+			
	1	2	3	p-value	1.1-2.0 low	2.1-4.0 moderate	≥4.1 high	p-value	0-3 day very early	4-7 day early	>7.0 day late	p-value
Frequency, n	88	78	58		30	51	134	-	74	85	65	-
Age (mean ± SD) (years)	63.5±15.6	64.5±12.5	64.8±15.2	0.83	62.2±18.2	66.2±11.9	63.5±14.6	0.48	65.8±13.6	64.9±15.1	61.5±14.4	0.18
Gender, F, n (%)	33 (37.5)	28 (35.9)	20 (34.5)	0.93	12 (41.4)	17 (33.3)	46 (34.3)	0.43	28 (37.8)	29 (34.1)	24 (36.9)	0.88
MV/NIV/HFNC (%)*	41 (46.6)	41 (52.6)	32 (55.2)	0.56	14 (48.3)	29 (56.9)	66 (49.3)	0.92	39 (52.7)	40 (47.1)	35 (53.8)	0.67
30-day in-hospital mortality n. (%)	38 (43.2)	35 (44.9)	28 (48.3)	0.83	11 (37.9)	27 (52.9)	57 (42.5)	0.45	37 (50)	34 (40)	30 (46.2)	0.44

*MV: Mechanical ventilator, NIV: non-invasive mechanical ventilator, HFNC: high flow nasal cannula, CP: convalescent plasma, SD: standard deviation, PCR: polymerase chain reaction, Ig: immunoglobulin

hand, Joyner et al. (34) reported in a retrospective analysis of 3,082 COVID-19 patients who were hospitalized and needed no mechanical ventilation that the transfusion of CP containing high anti-SARS-CoV-2 IgG antibody levels was associated with lower mortality (34). Other studies also support the use of CP to reduce in-hospital mortality and emphasize the need for relevant studies (35,36). In December 2021, although World Health Organization revised the survival guide on COVID-19 treatments as "in addition to its high costs, CP does not improve survival or reduce the need for mechanical ventilation", citing evidence that CP does not provide benefit to patients with non-severe COVID-19, it recommends that randomized clinical trials should continue in severe and critically ill patients (37). In this retrospective cohort study, we evaluated the impact of CP use on survival in patients with severe or critical COVID-19. Advanced age and male sex are associated with mortality as the most important risk factors for developing infection and progression to severe disease in COVID-19 patients (38). Other risk factors are cardiovascular disease, obesity, HT, diabetes mellitus (DM), chronic respiratory tract disease, CRF, cancer, and weakened immune status (5,39-41). In our study, male sex was at the forefront, and the mean age was significantly higher in the deceased group. No significant difference was detected between genders regarding respiratory support, whereas the need for invasive and non-invasive respiratory support statistically increased with advanced age. The most common comorbid diseases in patients with critical and severe COVID-19 were HT/CHF, followed by DM.

In a meta-analysis evaluating the administration time of CP, patients who received CP in the first 10 days of hospitalization were compared with those who received it between 10 and 20 days. Mortality was found to be decreased in those who received CP in the first ten days, however this decrease was not statistically significant (42). However, Salazar et al. (43) showed that mortality in patients who received CP within 72 hours of hospital admission was lower than that in those who received it late. In our study, the mean time to CP administration after the first PCR positivity was 5.893.95± days, and no significant difference was detected between the survivor and deceased patient groups. Furthermore, in our cohort, CP administration within 72 hours of PCR positivity had no impact on mortality and the need for respiratory support.

The efficacy of passive antibody therapy was associated with the concentration of neutralizing antibodies in the

Table 5. SOFA scores of the ICU patients in the groups created based on the power of the EI IgG ELISA of the first administered CP					
		Low 1.1-2.0	**Moderate 2.1-4.0**	**High >4.10**	**p-value**
SOFA* score (mean ± SD)	Hospitalization day	n=19 3.68±2.0	n=39 4.41±2.78	n=98 3.98±2.36	0.645
	CP baseline	n=19 4.84±2.71	n=39 5.67±3.1	n=99 4.83±2.5	0.351
	Day 5	n=16 3.75±3.06	n=27 5.41±3.21	n=91 4.79±2.88	0.223
*: The sequential organ failure assessment score, SD: standard deviation, ICU: intensive care unit, CP: convalescent plasma, Ig: immunoglobulin					

Table 6. Distribution of CP induced complications				
Complication	**Survivor group (n=123)**	**Deceased group (n=101)**	**Total (n=224) (%)**	**p-value**
Fever (baseline >1 °C)	1	7	8 (3.5)	
Allergic reaction	0	0	0	
TRALI	1	1	2 (0.8)	
TACO	0	1	1 (0.4)	
ADE	0	0	0	
Total	2	9	11 (4.9)	0.061
TRALI: Transfusion-related acute lung injury, TACO: transfusion-associated circulatory overload, ADE: antibody-dependent enhancement, CP: convalescent plasma				

plasma of recovered donors. The target titer recommendation of the European Commission for the neutralization test in COVID-19 CP is 1:320. Although the ability to demonstrate the neutralization performance of antibodies in SARS-CoV-2 CP is considered the gold standard, it is not easy to routinely perform tests intended for this purpose because they require a laboratory with a high biosafety level and experienced staff. Euroimmun IgG has been shown to correlate with neutralization assays (44-46). The FDA has stated that CP with a Euroimmun sample to the cutoff of ≥3.5 can be used to treat hospitalized patients (47).

It has been determined in many studies that the efficacy of CP treatment is linked to the SARS-CoV-2 antibody titer it contains (34,48). In a multicenter study, administration of CP with a high antibody titer before seven days was associated with low mortality (49). A randomized controlled clinical study conducted with an outpatient elderly population indicated that CP with a high antibody titer administered within 72 hours of the onset of COVID-19 symptoms improves clinical outcomes compared with placebo (50). However, the RECOVERY study involving 11,558 inpatients showed no difference in mortality risk between patients who received high antibody titers and those who received standard CP treatment (30). We did not observe a difference in mortality and the need for respiratory support among patients who received CP with an IgG ratio >4.0. The optimal dose and timing of CP treatment remains unclear (51). On the other hand, although the dosage is not standardized in CP administration in clinical practice, administering 200-500 mL CP in one or two regimens is generally accepted approach (42). In our study, there was no significant difference between patients administered 1, 2, and 3 units of CP (200-400-600 mL) regarding mortality and the need for respiratory support.

In their retrospective study, which included 117 COVID-19 inpatients, Yang et al. (52) reported that the SOFA score can be an independent risk factor for in-hospital mortality and can be used to evaluate COVID-19 severity and prognosis. However, Raschke et al. (53) showed that the SOFA score has a low mortality predictive accuracy in ventilator triage among patients with COVID-19, and they associated this with the fact that severe single organ dysfunction causes only a minimal change in SOFA scores. In our study, the SOFA scores were significantly higher in the deceased group than in the survivor group. Nonetheless, there were no significant differences in SOFA scores at baseline and day 5 of CP administration between the groups based on the antibody ratio of CPs administered.

The hyperinflammation associated with COVID-19 is similar to the symptoms of MAS, the clinical features of which have been previously reported. Increased serum ferritin, CRP, and D-dimer levels and decreased fibrinogen and platelet counts in patients with COVID-19 indicate the development of severe MAS-like inflammation and fibrinolysis (41,54). The inflammatory cascade, complement activation, and pro-inflammatory cytokines determine the course of the disease in COVID-19 patients. It has been stated that specific hematological and inflammatory biochemical laboratory parameters correlate with the severity of COVID-19 (55-57). Among the inflammatory markers, CRP has been found to increase significantly in the initial stages of infection in patients with COVID-19 and is considered an early marker for severe COVID-19 (58,59). In a prospective study evaluating 267 patients with severe COVID-19 who received CP, a decrease in CRP, ferritin, and interleukin-6 levels was determined (60). Higher and persistent inflammation markers and lower platelet counts were also associated with a poor prognosis in our cohort. Nevertheless, there was no consistent effect of CP administration on hyperinflammatory markers during follow-up was not observed. No similar studies have investigated the relationship between the changes in the laboratory parameters evaluated in our study and the power of the IgG ratio. Therefore, our study is of importance.

Although CP administration is generally considered safe and effective, it can cause some adverse events. Limited information is available regarding the specific side effects of CP therapy. However, the reported symptoms, including fever, chills, allergic reactions, TRALI, and TACO, are similar to those of other types of plasma blood components (61,25). The causes of the highest mortality risk following plasma transfusion are TRALI and TACO, possibly due to the sequelae of pulmonary complications (62). Theoretical concerns regarding the use of CP in patients with COVID-19 include a clinical condition that worsens after plasma transfusion due to antibody-dependent enhancement (ADE) or antibody-mediated pro-inflammatory effects. Joyner et al. (11) evaluated 5,000 patients with severe and critical COVID-19 regarding side effects after CP considering that respiratory problems due to COVID-19 may increase CP-associated complications. They detected less than 1% serious adverse events, 0.22% TRALI, 0.1% TACO, and 0.06% severe allergic reactions within the first 4 hours. Since the incidences of TRALI and TACO are expected to be approximately 10% in critically ill patients, the authors assessed CP treatment as reassuring due to their cohort's lower TRALI and TACO incidence rates (11). The incidence of TRALI and TACO in our study is in line with the literature, and there was no mortality due to CP-induced complications. However, the presence of many comorbidities in the patient group and vascular and pulmonary involvement caused by COVID-19 made the differential diagnosis of CP-related TRALI and TACO difficult. The specific signs and symptoms of COVID-19-induced ADE are unknown, and clinical deterioration and worse outcomes following CP administration can be associated with ADE. In our study, ADE was not suspected.

Conclusion

The retrospective nature of our study and the use of multiple drugs (antibiotic, antiviral, corticosteroid, anti-cytokines, low molecular weight heparin) in the individualized treatment of patients are limiting factors, which make it difficult to differentiate the laboratory/clinical impact of CP in severe/critical COVID-19 patients.

In conclusion, under the conditions of this retrospective cohort study, CP treatment was not associated with improved survival or other positive clinical outcomes in patients with severe/critical COVID-19. There is a need for more comprehensive and prospective controlled studies that can demonstrate the efficacy of CP in patients with COVID-19.

Ethics

Ethics Committee Approval: This single-center retrospective study was conducted at Ege University Hospital after receiving approval from the Clinical Research Ethics Committee (number: 20-5T/48).

Informed Consent: Donors were approximately 18-55 years, and all provided written informed consent at the time of plasmapheresis.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., İ.Ç., A.T., M.S.T., H.A.E., K.D., M.U., Y.A., Concept: Ö.Ö., İ.Ç., H.A.E., K.D., M.U., Y.A., Design: Ö.Ö., İ.Ç., M.S.T., K.D., M.U., Y.A., Data Collection or Processing: Ö.Ö., İ.Ç., A.T., H.A.E., Y.A., Analysis or Interpretation: Ö.Ö., İ.Ç., A.T., M.S.T., H.A.E., P.K., K.D., M.U., T.Y., Y.A., Literature Search: Ö.Ö., İ.Ç., A.T., M.S.T., K.D., M.U., Y.A., Writing: Ö.Ö., İ.Ç., A.T., M.S.T., H.A.E., P.K., K.D., M.U., T.Y., Y.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-3.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
3. World Health Organization, Coronavirus disease (COVID-19) Pandemic. Available from: https://www. who.int/emergencies/diseases/novel-coronavirus-2019. Accessed: 11 March 2020.
4. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi. 2020 F;41:145-51. Chinese.
5. World Health Organization (WHO). Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19); February 2020. Available at: www.who.int/docs/default-source/ coronaviruse/who-china-joint-mission-on-covid-19-final-report.
6. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA. 2020;324:782-93.
7. Alhazzani W, Evans L, Alshamsi F, Møller MH, Ostermann M, Prescott HC, et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Crit Care Med. 2021;49:219-34.
8. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005;24:44-6.
9. Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis. 2011;52:447-56.
10. Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther. 2018;23:617-22.
11. Joyner MJ, Wright RS, Fairweather D, Senfeld JW, Burno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. J Clin Invest 2020;130:4791-7.
12. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial JAMA. 2020;324:460-70. Erratum in: JAMA. 2020;324:519.
13. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 2020;323:1582-9.
14. Casadevall A, Pirofski LA. The convalescent sera option for contain - ing COVID-19. J Clin Invest. 2020;130:1545-8.
15. https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment https://www.fda.gov/media/141480/download
16. Turkish Republic Ministry of Health, General Directorate of Public Health, COVID-19 (SARS-CoV-2 Infection) Guide (Scientific com - mittee study), April 14, 2020. Available at: https://covid19bilgi.saglik. gov.tr.
17. Wong CKH, Lau KTK, Au ICH, Xiong X, Chung MSH, Lau EHY, et al. Optimal timing of remdesivir initiation in hospitalized patients with coronavirus disease 2019 (COVID-19) administered with dexamethasone. Clin Infect Dis. 2022;75:e499-e508.
18. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed: 03.03.2022
19. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397:1637-45.
20. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021;9:1407-18. Erratum in: Lancet Respir Med. 2021;9:e102.
21. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et. al; STOP-COVID trial investigators. tofacitinib in patients hospitalized with Covid-19 pneumonia. N Engl J Med. 2021;385:406-15.
22. REMAP-CAP Investigators; Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. N Engl J Med. 2021;384:1491-502.
23. Centers for Disease Control and Prevention (CDC). Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). Available at: www.cdc.gov/ coronavirus/2019-ncov/hcp/clinical-guidance-managementpatients.html (accessed: 22 March 2021)
24. World Health Organization (WHO). Clinical management of severe acute respiratory infection (SARI) when COVID19 disease is suspected: interim guidance. World Health Organization 2020;WHO/2019-nCoV/clinical/2020.4.
25. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med. 2006;17;145:599-609.
26. Eibl MM. History of immunoglobulin replacement. Immunol Allergy Clin North Am. 2008;28:737-64, viii.
27. Marson P, Cozza A, De Silvestro G. The true historical origin of convalescent plasma therapy. Transfus Apher Sci. 2020;59:102847.
28. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P. PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020;371:m3939.
29. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med. 2021;384:619-29.
30. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet. 2021;397:2049-59.
31. Bégin P, Callum J, Jamula E, Cook R, Heddle NM, Tinmouth A, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med. 2021;27:2012-24. doi: Erratum in: Nat Med. 2022;28:212.
32. Writing Committee for the REMAP-CAP Investigators; Estcourt LJ, Turgeon AF, McQuilten ZK, McVerry BJ, Al-Beidh F, Annane D, et al. Effect of Convalescent Plasma on Organ Support-Free Days

in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2021;326:1690-702.
33. Piechotta V, Iannizzi C, Chai KL, Valk SJ, Kimber C, Dorando E, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021;5:CD013600.
34. Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. N Engl J Med. 2021;384:1015-27.
35. O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest. 2021;131:e150646.
36. Arnold Egloff SA, Junglen A, Restivo JS, Wongskhaluang M, Martin C, Doshi P, et al. Convalescent plasma associates with reduced mortality and improved clinical trajectory in patients hospitalized with COVID-19. J Clin Invest. 2021;131:e151788.
37. 7th update of WHO's living guidelines on COVID-19 therapeutics. Available at: https://www.who.int/news/item/07-12-2021-who-recommends-against-the-use-of-convalescent-plasma-to-treat-covid-19
38. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262.
39. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20:398-400.
40. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
41. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180:934-43.
42. Wang Y, Huo P, Dai R, Lv X, Yuan S, Zhang Y, et al. Convalescent plasma may be a possible treatment for COVID-19: A systematic review. Int Immunopharmacol. 2021;91:107262.
43. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, et al. Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality. Am J Pathol. 2020;190:2290-303.
44. Weidner L, Gänsdorfer S, Unterweger S, Weseslindtner L, Drexler C, Farcet M, et al. Quantification of SARS-CoV-2 antibodies with eight commercially available immunoassays. J Clin Virol. 2020;129:104540.
45. Patel EU, Bloch EM, Clarke W, Hsieh YH, Boon D, Eby Y, et al. Comparative Performance of Five Commercially Available Serologic Assays To Detect Antibodies to SARS-CoV-2 and Identify Individuals with High Neutralizing Titers. J Clin Microbiol. 2021;59:e02257-20.
46. Walker GJ, Naing Z, Ospina Stella A, Yeang M, Caguicla J, Ramachandran V, et al. SARS Coronavirus-2 Microneutralisation and Commercial Serological Assays Correlated Closely for Some but Not All Enzyme Immunoassays. Viruses. 2021;13:247.
47. US Department of Health and Human Services Food and Drug Administration Letter of Authorization, Reissuance of Convalescent Plasma EUA. 2021. Available at: https://www.fda.gov/media/141477/download
48. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. J Med Virol. 2020;92:1475-83.
49. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv [Preprint].
50. Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. N Engl J Med. 2021;384:610-8.
51. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis. 2015;211:80-90.
52. Yang Z, Hu Q, Huang F, Xiong S, Sun Y. The prognostic value of the SOFA score in patients with COVID-19: A retrospective, observational study. Medicine (Baltimore). 2021;100:e26900.
53. Raschke RA, Agarwal S, Rangan P, Heise CW, Curry SC. Discriminant Accuracy of the SOFA Score for Determining the Probable Mortality of Patients With COVID-19 Pneumonia Requiring Mechanical Ventilation. JAMA. 2021;325:1469-70.
54. Otsuka R, Seino KI. Macrophage activation syndrome and COVID-19. Inflamm Regen. 2020;40:19.
55. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection-a review of immune changes in patients with viral pneumonia. Emerg Microbes Infect. 2020;9:727-32.
56. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020;55:102763.
57. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta. 2020;506:145-8.
58. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020;92:856-62.
59. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med. 2020 ;58:1021-8.
60. Fodor E, Müller V, Iványi Z, Berki T, Kuten Pella O, et al. Early Transfusion of Convalescent Plasma Improves the Clinical Outcome in Severe SARS-CoV2 Infection. Infect Dis Ther. 2022;11:293-304. Erratum in: Infect Dis Ther. 2022;11:1767-8.
61. Chun S, Chung CR, Ha YE, Han TH, Ki CS, Kang ES, et al. Possible Transfusion-Related Acute Lung Injury Following Convalescent Plasma Transfusion in a Patient With Middle East Respiratory Syndrome. Ann Lab Med. 2016;36:393-5.
62. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. J Am Coll Cardiol. 2020;75:2352-71.

Turk J Intensive Care 2024;22:281-8
DOI: 10.4274/tybd.galenos.2023.03880

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Alev Öztaş,
Burcu İleri Fikri,
Zinet Aslancı,
Güldem Turan

Malignant Futility in the Intensive Care Unit

Yoğun Bakım Ünitesinde Malign Futilite

Received/Geliş Tarihi : 19.06.2023
Accepted/Kabul Tarihi : 30.11.2023

Alev Öztaş, Burcu İleri Fikri, Güldem Turan
University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Intensive Care, İstanbul, Turkey

Zinet Aslancı
University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Anaesthesiology and Reanimation, İstanbul, Turkey

Alev Öztaş MD (✉),
University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Intensive Care, İstanbul, Turkey

E-mail : alvoztas@gmail.com
ORCID ID : orcid.org/0000-0002-8423-6824

***The study was reported as an oral presentation at the Turkish Intensive Care Society Congress-2022.**

ABSTRACT *Objective:* The number of oncological patients whose life expectancy has been prolonged thanks to the developments in diagnosis and treatment modalities in the intensive care unit (ICU) is increasing. One of the most common reasons for ethics committee consultation is that patients and their families demand unnecessary restraint from doctors. Although clinical criteria are used to decide whether the applied treatment is useless, it is not sufficient alone to overcome the problems in this regard. The first aim of this study is to draw attention to the futil therapy applied in patients with terminal malignancies in our country and to help determine the necessary strategies to reduce the futility rate. The second purpose is to determine the cost of the futil therapy applied in the intensive care to the health system.
Materials and Methods: The data of 127 patients with malignancy who were followed up in the ICU between 01 December 2020 and 31 December 2021 were analyzed retrospectively. Stage-4 patients aged 18 years or older with a diagnosis of malignancy, who were recommended palliative treatment by oncologists, and with inoperable, terminal stage, metastatic malignancy were considered as patients who received futile treatment and were included in this study.
Results: Futil treatment was observed in 98 of 127 oncological patients treated in the ICU, and the mortality rate was 86.73% (n=85) in these patients.The cost of futile treatment to the health system was 1.071 intensive care days and $187,907.4 for these patients, who had a high mortality rate, during their stay in the ICU.
Conclusion: With the relevant legal regulations to be made, the evaluation of terminal stage oncological patients by the ethics consultants and the determination of care protocols, and the opening of intermediary ICUs, it can be ensured that patients will have more qualified lifetime.
Keywords: Cost-effective, intensive care, futility, malignancy

ÖZ *Amaç:* Yoğun bakım ünitelerinde (YBÜ) tanı ve tedavi yöntemlerindeki gelişmeler sayesinde yaşam süresi uzamış olan onkolojik hasta sayısı artmaktadır. Hasta ve ailelerinin hekimlerin yararsız bulduğu tedaviyi talep etmeleri, en yaygın etik kurul konsültasyon nedenlerinden biridir. Uygulanan tedavinin yararsız olup olmadığına karar vermek için her ne kadar klinik kriterler kullanılsa da bu konudaki sorunların aşılmasında tek başına yeterli değildir. Bu çalışmanın birinci amacı ülkemizdeki terminal dönem maligniteli hastalarda uygulanan futil tedaviye dikkat çekerek futilite oranını azaltmak için gerekli stratejileri belirlemeye yardımcı olmak, ikinci amacı ise YBÜ'de uygulanan futil tedavinin sağlık sistemine getirdiği maliyeti belirlemektir.
Gereç ve Yöntem: 01 Aralık 2020-31 Aralık 2021 tarihleri arasında yoğun bakımda takip edilen maligniteli 127 hastanın verileri retrospektif olarak incelendi. On sekiz yaş ve üzeri malignite tanılı, onkologlar tarafından palyatif tedavi önerilen, inoperabl, terminal evre, metastatik malignitesi olan Evre-4 hastalar, nafile tedavi alan hastalar olarak kabul edilerek bu çalışmaya dahil edildi.
Bulgular: YBÜ de tedavi edilen 127 onkolojik hastanın 98'ine futil tedavi uygulandığı görüldü ve bu hastalarda mortalite oranı %86,73 (n=85) olarak tespit edildi. Mortalite oranı yüksek olan bu hastaların yoğun bakımda yattıkları süre boyunca nafile tedavinin sağlık sistemine maliyeti 1,071 yoğun bakım günü ve 187.907,4$ idi.
Sonuç: Yapılacak ilgili yasal düzenlemeler ile etik konsültanları tarafından terminal dönem onkolojik hastaların değerlendirilerek bakım protokollerinin belirlenmesi ile birlikte ara YBÜ'lerinin açılması ile hastaların yaşamlarının son dönemini kaliteli bir şekilde geçirmesi sağlanabilir.
Anahtar Kelimeler: Maliyet, yoğun bakım ünitesi, futilite, malignite

Introduction

Intensive care units (ICUs) are medical units with advanced technology, advanced life support, are fully equipped, and are high cost, where doctors, nurses, and allied health personnel serve. Patient admission to the ICU was based on clinical and physiological criteria (1).

The number of oncological patients whose life expectancy has been prolonged because of developments in diagnosis and treatment modalities in the ICU is increasing daily. Indications for admission to the ICU in this patient group often include reasons such as postoperative period, respiratory failure, infection, and sepsis (2).

Although there are scoring systems, such as acute physiologic, chronic health evaluation (APACHE), and simplified acute physiology score, that predict the survival of patients admitted to the ICU, there is still no specific scoring system that predicts the survival of oncologic patients in the ICU. While clinical conditions, such as disease stage, treatments, developing organ failure, mechanical ventilator, and vasopressor, support determine life expectancy in ICU in oncological patients (2). The Eastern Cooperative Oncology Group performance score and karnofsky performance status score (Table 1), which are prevalently used to determine the functional status of patients, also play a role in the treatment and palliative care plan. In addition, studies using these scoring systems have revealed that poor performance status is associated with mortality (3,4).

The willingness of patients and their families to ask for treatment that physicians consider futile is one of the most common reasons for ethics committee consultations (5). Although clinical criteria, such as the inability of the treatment to achieve the goal, imminent death, and the inability of the patient to survive outside of the ICU, are used to decide whether the applied treatment is futile, it is not sufficient alone in overcoming the problems within this regard (6). Hence, in some countries, conflicts between the patient, patient's family, and physicians have been averted by legal regulations. However, in many countries worldwide, futile treatment has not been fully elucidated. Within the framework of the traditions, customs, and religious beliefs of the societies, the relatives of the patients want their patients to be given full support until the last moment (7). Meanwhile, in our country, due to their legal responsibilities, intensive care specialists cannot refuse patients who require supportive treatment. To prevent patients and their relatives from suffering from the problems experienced, follow-up and treatment continued in the ICU; thereby, the futile treatment rate increased, and the rational use of ICU beds was avoided.

The primary objective of this study was to remark on futile treatment implemented in patients with terminal malignancies in our country and to help determine the necessary strategies to reduce the futility rate. The second objective is to determine the cost of futile treatment implemented in the ICU to the health system.

Materials and Methods

In our study, the data of malignant patients followed in Level 3 ICU between December 01, 2020 and December 01, 2021 were retrospectively reviewed. Stage 4 patients aged 18 years and older, diagnosed with malignancy, who received palliative treatment recommended by oncologists,

Table 1. Karnofsky performance scoring

Progression	Criteria	Score (%)
Able to carry on normal activity and to work; no special care needed	Normal no complaints; no evidence of disease	100
	Able to carry on normal activity; minor signs or symptoms of disease	90
	Normal activity with effort; some signs or symptoms of disease	80
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	Cares for self; unable to carry on normal activity or to do active work	70
	Requires occasional assistance, but is able to car efor most of his personal needs.	60
	Requires considerable assistance and frequent medical care.	50
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	Disabled; requires special care and assistance	40
	Severely disabled; hospital admission is indicated although death not imminent	30
	Very sick; hospital admission necessary; active supportive treatment necessary.	20
	Moribund; fatal processes progressing rapidly	10
	Dead	0

with inoperable, terminal stage, metastatic malignancy were considered to be patients receiving futile treatment and were included in the present study (Figure 1). Patients with newly diagnosed malignancy, patients who received chemotherapy, radiotherapy, and/or surgical treatment within a month before hospitalization in the ICU, patients who were in remission after malignancy treatment, and patients with malignancy but who were hospitalized in the ICU for reasons independent of malignancy, such as coronavirus disease-2019 (COVID-19), were excluded from this study.

Demographic characteristics of the patients, type of malignancy, APACHE II, sequential organ failure assessment score (SOFA), and Karnofsky performance status score, where and with what symptoms the patients who received futile therapy were admitted to the ICU, and if available in the file records, whether the relatives of the patients requested the treatment were noted. We examined whether patients underwent cardiopulmonary resuscitation (CPR) and intubation without CPR before admission to the ICU. Intubated patients were evaluated in three categories: Intubation before admission, intubation within the first 24 hours, and intubation during follow-up in the ICU. Patients who were intubated before admission were divided into two subgroups: Those with and without CPR. The association between intubation and CPR and mortality was analyzed.

Invasive procedures, such as central vein and artery catheterization, continuous renal replacement therapy (CRRT), tracheostomy, mechanical ventilator (MV) application, radiological imaging, number of consultations ordered for the relevant clinics for treatment and services for transplantation, duration of ICU stay, way the patients exited the ICU was evaluated as discharge to the ward, discharge to the palliative service, and exitus. The 30- and 90-day mortality rates were also analyzed.

The cost calculation was made in accordance with the Healthcare Implementation Communiqué (SUT) payments directive of the TR Ministry of Health, which was mandated on May 01, 2022, considering interventional procedures, other unit consultations, and radiological imaging. Basic patient care practices, such as laboratory, medication, and materials, were not included in the cost calculation.

The present study was approved by the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (no: 49, date: 09/02/2022).

Statistical Analysis

Statistical data were obtained using IBM SPSS Statistics 20 software, and data were expressed as numbers, percentages, and mean ± standard deviation.

Results

In this study, 29 of the 127 oncological patients treated in the ICU were excluded because they were not considered to be receiving futile treatment. Of the 98 patients considered to be receiving futile therapy, 37 (37.76%) were female and

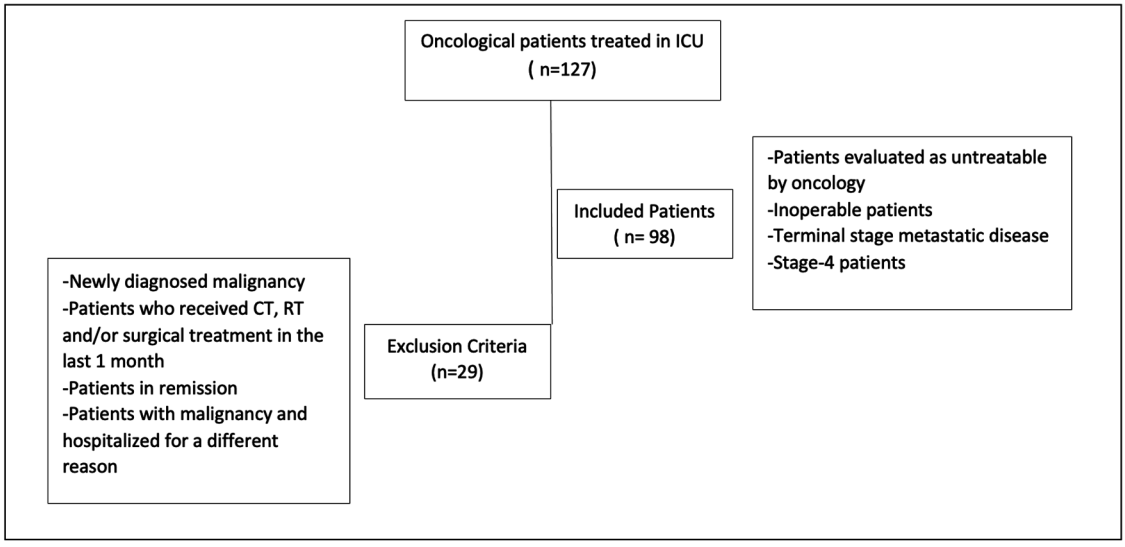

Figure 1. Flowchart of patient selection
n: Number, CT: chemotherapy, RT: radiotherapy, ICU: intensive care unit

61 (62.24%) were male. The mean age of female patients was 61.97 years, whereas the mean age of male patients was 62.49 years (Table 2).

It was determined from the files of eight patients admitted from the emergency department (n=2) and clinical services (n=6) that they and their relatives did not want to continue treatment. Four of these patients underwent CPR. No information on this subject was found in the files of the remaining 90 patients.

The patients were mostly admitted to the ICU from the clinical services, and the most common types of malignancy belonged to the lung and gastrointestinal tract (Table 2).

Table 2. Demographic characteristics, diagnoses, and scoring of patients

Patient sex	**Number of people (%)**	**Mean age (min-max)**
Female	37 (37.76%)	61.97±17.92 (27-93)
Male	61 (62.24%)	**62.49**±13.04 (18-88)
Patient source		
Lung	30 (30.61%)	62.63±12.44 (32-87)
GIS	21 (21.42%)	68.14±12.98 (36-88)
Intra-abdominal solid	9 (9.18%)	71.33±10.40 (57-93)
Hematology	9 (9.18%)	65.44±14.20 (46-89)
Gynecologic	8 (8.16%)	57±14.50 (42-89)
Breast	7 (7.14%)	51.71±19.6 (27-88)
Suprarenal-renal	5 (5.10%)	55.2±14.82 (32-72)
Prostate	1 (1.02%)	66
Brain	2 (2.04%)	40.5±31.82 (18-63)
Thyroid	1 (1.02%)	29
Larynx	1 (1.02%)	62
other	4 (4.08%)	58±16.49 (40-72)
Patient admission		
Emergency	31 (31.63%)	**64.45±12.62** (32-89)
Clinic	65 (66.33%)	61.45**±**16.13 (18-93)
Palliative	2 (2.04%)	56.5**±**9.19 (50-63)
Scoring		
APACHE- II (mean ± SD)	24.97**±9.81 (10-51)**	
SOFA (mean ± SD)	10.79**±4.86 (2-21)**	
Karnofsky score	25 (25.51%)	10 points
	52 (53.06%)	20 points
	21 (21.43%)	30 points

GIS: Gastrointestinal system, APACHE-II: acute physiological and chronic health evaluation-II, SOFA: sequential organ failure assessment, SD: standard deviation

Karnofsky's performance status score ranged from 10 to 30 points. The main reasons for admission to the ICU were respiratory failure (n=26) and, to a lesser extent, impaired consciousness (n=10), hypotension (n=7), sepsis (n=7), and metabolic disorders (n=9). Among the included patients, 33.6% were admitted to the ICU as intubated, whereas 18.3% were admitted to the ICU after CPR. The reasons for intubation included desaturation, hemoptysis, low Glasgow Coma scale, and hemodynamic instability. Thirty patients admitted to the ICU were intubated within the first 24 hours, and 23 were intubated during the treatment period. In 12 patients, an invasive MV was not required. The ICU stay was 3-28 days in non-intubated patients, while it was 1-82 days in intubated patients (Table 3).

The mortality rate was 86.73% (n=85) in patients who received futile treatment, and 13 patients had more than one CPR application during their hospitalization. 90.59% (n= 77) of the deaths occurred in the first month, and 8.24% (n=7) occurred within 90 days. Of the patients who received futile therapy, 11.22% (n= 11) were transferred to clinical services and 2.04% (n=2) to the palliative service. The findings showed that four transferred patients died within the first 3 months, and six patients could not be followed up.

In total, 108 central vein catheterizations and 121 arterial cannulations were performed in 98 patients who received futile treatment. Tracheostomy was performed in six patients due to prolonged intubation duration. CRRT support was provided to 11 patients. The radiological imaging methods used and the number of consultations are presented in Table 4.

Health expenses for patients who received futile treatment were calculated according to the TR Ministry of Health SUT Annex-2/C and Annex-2/B, which were in effect on May 01, 2022. It was determined that 2.652.042 TL was spent for 1071 futile ICU days, 83.433 TL for 778 MV follow-up days, which were intubated and followed up with mechanical ventilator, 37.691 TL for invasive procedures, such as arterial and central venous intervention, CCRT, and tracheotomy, 5.386 TL was spent for radiological imaging, and 5.319 TL for consultations (Table 3).

Discussion

In the LST process of patients with oncology at the end of life with high mortality, the religious beliefs and cultural structures of societies are effective in the decision

Table 3. Scoring, MV, number of ICU days, mortality by intubation duration, and CPR					
	Intubated patients before ICU		ICU Within first 24 hours Intubated patients (n=30)	ICU 24 hours-treatment period intubated patients (n=23)	ICU Non-intubated patients (n=12)
	CPR (+), intubated patients (n=18)	CPR (-), intubated patients (n=15)			
Scoring					
APACHE-2 (mean ± SD)	32.78±10.23	27.87±9.52	26.3±9.01	17.52±8.63	14±7.58
SOFA (mean ± SD)	12.95±3.69	11.93±3.67	12.2±4.51	9.48±4.77	4.92±4.34
Karnofsky score/n	20/3 10/5	20/10 10/5	30/1 20/25 10/4	30/12 20/10 10/1	30/8 20/4
Mean number of days with MV ± SD (min-max)	6.22±8.76 (1-29)	14.33±23.94 (1-82)	9.57±13.45 (1-57)	7.04±13.51 (0-61)	
Mean number of ICU days ± SD (min-max)	6.22±8.76 (1-29)	14.33±23.94(1-82)	10.53±14.8 (1-68)	12.7±15.38 (2-67)	11.33±7.94 (3-28)
Mortality					
1st month	18 (100%)	12 (80%)	27 (90%)	20 (86.96%)	2 (16.67%)
1st-3rd months	0	3 (20%)	1 (3.33%)	3 (13.04%)	3 (25%)
ICU mortality	18 (100%)	15 (100%)	28 (93.3%)	23 (100%)	1 (8.3%)

ICU: Intensive care unit, n: number of patients, CPR: cardioplumober resuscitation, APACHE-II: acute physiological and chronic health evaluation-II, SOFA: sequential organ failure assessment, MV: mechanical ventilator, SD: standard deviation

Table 4. Special procedures applied to futile therapy patients and their costs			
The procedure	**Total number (min-max/for a patient)**	**Unit price**	**Total price**
Number of Level 3 ICU days	1071 (1-82)	2.476,23	2.652.042
Number of intubation	53 (0-1)	44,49	2.357
Number of MV connection	53 (0-1)	66,52	3.525
Number of days with MV	778 (0-82)	99,68	77.551
Number of intraarterial cannulation	121 (1-2)	133,04	16.097
Number of central vein catheterization	108 (1-3)	150,04	16.204
Number of CRRT	11 (0-1)	179,14	1.970
Number of tracheotomy	6 (0-1)	570,15	3.420
Number of direct radiography	242 (0- 19)	18,45	4.464
Number of computerised tomography	5 (0-1)	149,25	746
Number of magnetic resonance imagining	1 (0-1)	176,40	176
Number of CPR	98 (0-2)	354,49	34.740
Number of ordered total consultation	308 (0-26)	17,27	5.319
Total cost (TL)			2.818.611

ICU: Intensive care unit, MV: mechanical ventilator, CRRT: continuous renal replacement therapy, CPR: cardiopulmonary resuscitation, TL: Turkish lira

to continue or discontinue treatment. The absence of relevant legal regulations prevents families and physicians from making clear decisions (8). Countries have varying approaches to withdrawal and discontinuation of treatment. However, in our country, legal regulations on this issue are inadequate. Thus, while ICU physicians cannot refuse to accept patients who require supportive treatment, physicians from other branches think and demand that patients in need of palliative care should be followed in ICU due to potential legal problems. In our ICUs, all patient relatives are informed about the process and futile treatment during the terminal period of the disease. However, since it is not legally possible to discontinue treatment, the relatives of patients are not asked whether they want to continue the treatment.

The relatives of patients often want their patients to be given all the support until the last moment, within the framework of the traditions, customs, and religious beliefs of our society. However, we found in the files of eight patients that their relatives wanted the treatment terminated. With the entry into force of the Leonetti law in France, the limits of LST were determined legally. Blythe et al. (7) evaluated post-legal LST in their study among physicians and nurses and reported that the decisions taken by the clear determination of the treatment limits by discussion by the team members involved in the treatment were reliable and applicable to the participants. We found that 77.17% of the patients with malignancy who were followed-up in the ICU at our hospital received futile treatment. All patients underwent an aggressive intensive care follow-up period, and 90.59% died in the first month, whereas 98.83% died within three months. Hence, with legal regulations, it is possible for patients and their relatives to have a say in the continuity of treatment in terminal oncological patients with high mortality. Moreover, the dimensions of futile treatment can be reduced by assessing patients before admission to the ICU with an ethics committee to be established in hospitals.

Advances in fully equipped ICUs and the availability of intensive care physicians are increasing the number of lives saved and the life expectancy of patients. Advanced stage, multiple organ failure, high APACHE-II, and poor performance status adversely affect the prognosis in patients with malignancy followed in the ICU (2). Likewise, in our study, we found that patients with a high APACHE- II score, SOFA score, and Karnofsky performance scale score of ≤30 had a poor prognosis. Kılınç et al. (9), in their study evaluating the prognosis in cancer patients treated in the ICU, also determined the mortality rate as 89.2%. Similarly, we determined the mortality rate as 86.73% in oncological patients receiving futile therapy. We observed that all oncological patients admitted to the ICU after being intubated were mortal. The mortality rate was 93.3% in patients who were intubated within the first 24 hours after hospitalization and 100% in patients who were intubated later on. Although performing CPR in patients with metastatic cancer has contradictory results on survival (10,11), in our study, all patients (n=21) who underwent CPR after cardiac arrest died within the first month after ICU admission.

Lee et al. (12) from South Korea also revealed in their study that with the well-dying law, families can spend much longer time with the patient, allow doctors to limit life-sustaining treatment, improve the quality of death in the ICU, and the time from DNR to death is longer. It was planned to transfer 17 terminal patients with stable vital parameters in the ICU who did not need supportive treatment to clinical and palliative services so that they could spend more time with their relatives at good quality. However, 62 consultations (min: 1, max: 10) were required to achieve this transfer, and unfortunately, five patients (min: 1, max: 6) died before they could be transferred from the ICU. Undoubtedly, the insufficient number of palliative care units (PCUs) was the most important reason for the observed situation. However, in our study, patients who were followed up in PCUs during the end-of-life period were admitted to the ICU. This suggests the necessity of an intermediary ICU, which is better equipped than palliative services, where less invasive procedures are applied to the patients, is more comfortable, and has a team experienced in terminal malignancies.

The cost of futile treatment during the time these patients with high mortality spent in the ICU was 1071 futile ICU days and 2.652.042 TL. TL was 2.476 TL in one ICU day and 2.575 TL in an ICU day for patients who were intubated and followed up on a ventilator. In addition to providing arterial and vein catheterization to all patients during follow-up, CRRT support was provided to eight patients with hemodynamic instability and renal failure. Percutaneous tracheostomy was performed in six patients due to prolonged intubation duration. The cost of these invasive procedures was 37.691 TL. However, we did not include standard palliative care services, such as nasogastric feeding, pressure ulcer treatment, and antibiotherapy, when calculating the cost. Our aim was to determine the cost resulting from specific procedures performed in the ICU. Huynh et al. determined

the cost of 464-day futile treatment of 123 patients followed in the ICU to be roughly 2.6 million dollars (6). Aygencel and Türkoğlu, on the other hand, determined in their study that 83 patients with terminal malignancies cost the healthcare system 581.353,2 TL in 858 ICU days, 677,6 TL per day (13). In the study conducted on oncological patients in Saudi Arabia, the care goals of the patients were determined beforehand, and obligatory recording of the care goals of the patients in the electronic environment was ensured. Ultimately, it was determined that ICU hospitalizations in patients with cancer treated for palliative purposes decreased from 26% to 12%, and some $777.600 was saved annually (14). In our study, the findings showed that as a result of the specific procedures applied to 98 patients who received futile treatment in the ICU, the cost to the health system was approximately 2.818.611 TL ($1=15 TL, $187.907,4) and that if these patients are cared for in the PCU (PCU 927,94 TL/day), approximately 1.824.788 TL ($121.652,5) can be saved. The treatment costs may vary between hospitals and countries. However, it is common worldwide that aggressive treatments and procedures applied in the ICU do not help patients who spend the last days of their lives away from their relatives. This study supports other studies analyzing the economic dimension of futile medical care provided to patients who have no opportunity for treatment (15,16).

Study Limitations

The limitation of our study is that it was a single-center, retrospective, and planned study during the pandemic. Since most ICU beds were allocated for COVID-19-infected patients during the pandemic, the futility rate in malignant patients seems to be relatively low. Moreover, as patients and their relatives could not be asked for legal reasons regarding whether they demanded treatment continuity, we could not obtain a sufficient number of them in our records.

Conclusion

In conclusion, the rate of futile treatment is increasing due to families' insistence on advanced treatment, physicians' belief that this group of patients should end their lives in the ICU, and the lack of legal regulations. With the relevant legal regulations to be established, the evaluation of terminal-stage oncological patients by ethics consultants, the determination of care protocols, and the opening of intermediary ICUs can ensure that patients spend the last period of their lives with less invasive procedures with a more experienced team. Thus, we believe that the cost of futile treatment to the healthcare system may decrease, physicians will be less exposed to the psychological trauma caused by malpractise-compensation cases, and ICU provision may be easier for patients with a higher chance of survival.

Ethics

Ethics Committee Approval: The present study was approved by the Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital (no: 49, date: 09/02/2022).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Ö., B.İ.F., G.T., Concept: A.Ö., G.T., Design: A.Ö., G.T., Data Collection or Processing: A.Ö., B.İ.F., Z.A., Analysis or Interpretation: A.Ö., G.T., Literature Search: A.Ö., B.İ.F., G.T., Writing: A.Ö., B.İ.F., Z.A., G.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Nates JL, Nunnally M, Kleinpell R, Blosser S, Goldner J, Birriel B, et al. ICU admission, discharge, and triage guidelines: a framework to enhance clinical operations, development of ınstitutional policies, and further research. Crit Care Med. 2016;44:1553-602.
2. Kostakou E, Rovina N, Kyriakopoulou M, Koulouris NG, Koutsoukou A. Critically ill cancer patient in intensive care unit: issues that arise. J Crit Care. 2014;29:817-22.
3. De Camargo JD, Delponte V, Costa AZS, da Silva Souza RC. Survival of cancer patients under treatment with the palliative care team in a Brazilian hospital in São Paulo. Can Oncol Nurs J. 2022;32:182-9.
4. Van der Zee EN, Noordhuis LM, Epker JL, van Leeuwen N, Wijnhoven BPL, Benoit DD, et al. Assessment of mortality and performance status in critically ill cancer patients: A retrospective cohort study. PLoS One. 2021;16:e0252771.
5. Pope TM. Medical Futility. Hester DM, Schonfeld t (editors). Guidance for Healthcare Ethics Committees. Cambridge University Press, Cambridge, UK: 2012. Ch. 12.pp. 88-97.
6. Huynh TN, Kleerup EC, Wiley JF, Savitsky TD, Guse D, Garber BJ, et al. The frequency and cost of treatment perceived to be futile in critical care. JAMA Intern Med. 2013;173:1887-94.
7. Blythe JA, Kentish-Barnes N, Debue AS, Dohan D, Azoulay E, Covinsky K, et al. An interprofessional process for the limitation of life-sustaining treatments at the end of life in France. J Pain Symptom Manage. 2022;63:160-70.
8. Dzeng E, Bein T, Curtis JR. The role of policy and law in shaping the ethics and quality of end-of-life care in intensive care. Intensive Care Med. 2022;48:352-4.
9. Kılınç G, Karaduman S, Sungurtekin H. Evaluation of the prognosis of cancer patients treated in intensive care units. J Turk Soc Intens Care. 2022;20:31-7.
10. Champigneulle B, Cariou A, Vincent F. Cardiopulmonary resuscitation and benefit to patients with metastatic cancer. JAMA Intern Med. 2016;176:142.
11. Schwarze ML, Nabozny MJ, Steffens NM. Cardiopulmonary resuscitation and benefit to patients with metastatic cancer–Reply. JAMA Intern Med. 2016;176:142-3.
12. Lee YJ, Ahn S, Cho JY, Park TY, Yun SY, Junghyun K, et al. Change in perception of the quality of death in the intensive care unit by healthcare workers associated with the implementation of the "well-dying law". Intensive Care Med. 2022;48:281-9.
13. Aygencel G, Turkoğlu M. General characteristics and costs of terminal stage patients in a medical intensive care unit. J Crit Intensive Care. 2014;5:1-4.
14. Salama H, Al Mutairi N, Damlaj M, Alolayan A, Binahmed A, Salama H, et al. Reducing futile acute care services for terminally ill patients with cancer: The dignity project. JCO Oncol Pract. 2021;17:1794-802.
15. Carter HE, Winch S, Barnett AG, Parker M, Gallois C, Willmott L, et al. Incidence, duration and cost of futile treatment in end-of-life hospital admissions to three Australian public-sector tertiary hospitals: a retrospective multicentre cohort study. BMJ Open. 2017;7:e017661.
16. Schouela N, Kyeremanteng K, Thompson LH, Neilipovitz D, Shamy M, D'Egidio G. Cost of futile ICU care in one Ontario hospital. Inquiry. 2021;58:469580211028577.

Turk J Intensive Care 2024;22:289-95
DOI: 10.4274/tybd.galenos.2023.03360

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

İnci Vetem Karagülle,
İsmail Kerem Gelir,
Birgül Büyükkıdan Yelken

Investigation of the Effect of Laboratory Values of ICU Patients Diagnosed with COVID-19 During Hospitalization on Their Symptoms After Discharge

COVID-19 Tanılı Yoğun Bakım Hastalarının Yatış Sürecindeki Laboratuar Değerlerinin Taburculuk Sonrası Semptomları Üzerine Etkisinin İncelenmesi

Received/Geliş Tarihi : 04.05.2023
Accepted/Kabul Tarihi : 06.12.2023

İnci Vetem Karagülle
Eskişehir Osmangazi University Faculty of Medicine, Department of Intensive Care Unit, Eskişehir, Turkey

İsmail Kerem Gelir
Yunus Emre State Hospital, Clinic of Intensive Care University, Eskişehir, Turkey

Birgül Büyükkıdan Yelken
Eskişehir Osmangazi University Faculty of Medicine, Department of Intensive Care Unit, Eskişehir, Turkey

İnci Vetem Karagülle MD (✉),
Eskişehir Osmangazi University Faculty of Medicine, Department of Intensive Care Unit, Eskişehir, Turkey

E-mail : incivetem@yahoo.com
ORCID ID : orcid.org/0000-0002-9250-0330

Presented in: This study was presented orally at the 21st National Intensive Care Congress.

ABSTRACT *Objective:* It is known that coronavirus infectious disease 2019 (COVID-19), patients continue to have symptoms, respiratory system insufficiency and loss of functional status in the post-COVID period after dischargefrom the hospital.
Materials and Methods: A total of 101 patients who werehospitalized in the intensive care unit and who could be questioned for their post-COVID symptoms at the1st and 3rd months after discharge from the hospital were included in this study.
Results: The most frequent symptom observed at the time of discharge was dyspnea (n=89), which has been found to be related to comorbidity, hypoxiaand hypertension. Moreover, it was observed thatat least 1 symptom persisted in 50 patients at the 3rd month of discharge, and the most frequentsymptom was fatigue and forgetfulness.
Conclusion: Taking into account the patients' risk factors, comorbidities and conditions during the hospitalization process, the process of transition to normal life after discharge can be accelerated with early discharge and more effective rehabilitation according to their functional status. Thus, labor loss can be prevented and costs can be reduced.
Keywords: Prolonged COVID-19, dyspnea, intensive care

ÖZ *Amaç:* Koronavirüs hastalığı-2019 (COVID-19) hastalarının taburculuk sonrası post COVID dönemde de semptomlarının devam ettiği, solunum sistemi yetersizliklerinin ve fonksiyonel durum kaybının olduğu bilinmektedir.
Gereç ve Yöntem: Yoğun bakım servisinde yatmış ve taburculuk sonrası 1. ay ve 3. ay post COVID semptom sorgulaması yapılabilen 101 hasta çalışmaya dahil edilmiştir.
Bulgular: Taburculuk esnasında en sık semptomdispne (n=89) olmuştur. Bu semptom komorbidite, hipoksi ve hipertansiyon ile ilgili bulunmuştur. Üçüncü ayda 50 hastada en az 1 semptomun devam ettiği ve en sık devam eden semptomun ise halsizlik ve unutkanlık olduğu görülmüştür.
Sonuç: Hastaların risk faktörleri, komorbiditeleri ve yatış sürecindeki durumları göz önüne alınarak erken taburculuk ve fonksiyonel durumlarına göre de daha etkin rehabilitasyon ile taburculuk sonrası normal hayata geçiş süreci hızlandırılabilir. Böylece iş gücü kaybı önlenerek, maliyet azaltılabilir.
Anahtar Kelimeler: Uzamış COVID-19, dispne, yoğun bakım

Introduction

Coronavirus infectious disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first detected in December 2019 in the city of Wuhan in China. The World Health Organization declared COVID-19 as a pandemic on March 11, 2020, when the first case was reported in Turkey (1). Although COVID-19 can be asymptomatic, it may lead to the development of extremely different clinical conditions, such as severe respiratory symptoms and extrapulmonary findings in addition to clinical conditions that may lead to death (2).

The term "prolonged COVID-19"was first used by Elisa Perego from Lombardy in Italy, to sum up the disease experience (3). It was described as the symptoms or signs that could be unexplained by an alternative diagnosis and which lasted for >12 weeks according to the National Institute for Health and Care Excellence guideline. In addition to this description, the prolonged COVID-19 term was later used to include both the continuing (Subacute 4-12 weeks) and post-COVID-19 (>12 weeks) period (4). Currently, the term "prolonged COVID-19" is used to refer to the disease in people not only whose effects of the infection continue despite having recovered but also whose symptoms continued to show for longer than the expected period (5).

According to the study by the King's College London, the risk factors for prolonged COVID-19 include advanced age, female gender, obesity and asthma (6). However, without an officially accepted definition of this post-COVID-19 state, there is no clear data on how long this state lasts, who is at risk, what factors lead to this condition, its pathophysiology, and how it can be treated and prevented through early diagnosis.

The most frequently reported symptoms of prolonged COVID are fatigue, shortness of breath, coughing, joint pain, and chest pain. The rare symptoms include difficulty in concentrating, depression, myalgia, headache, intermittent fever and palpitations (7). Although the time of regression of symptoms varies, it seems that the time until the complete disappearance of symptoms depends on both the severity of the acute illness and the spectrum of the symptoms experienced by the patient in addition to the pre-disease risk factors (8). In a study conducted in Switzerland, 669 patients (mainly outpatients) tested positive for COVID-19 and 32% of these patients continued to manifest at least one symptom on an average of 43 days after their discharge (9).

Routine biochemical, hematological, and immunochemical laboratory tests are important for the assessment of the severity of this disease, determining the appropriate treatment options, and pursuing the treatment response (10). Nevertheless, no specific parameter for the post-COVID period has been obtained so far and the number of relevant studies conducted on this subject is insufficient.

This study aimed to analyze the demographic data of patients with COVID-19 who were followed in the intensive care unit (ICU) and whose vital signs and laboratory values were recorded during the hospitalization stay so as to determine their effect on the clinical symptoms that continue after discharge, including respiratory failure and the degree of functional status. In addition, contributions to the literature studies on early discharge, mobilization, and rehabilitation were assessed with reference to the continuing symptoms and respiratory failure at home after discharge.

Material and Methods

Inour study, patients aged >18 years and whose diagnosis was confirmed by reverse transcriptase-polymerase chain reaction and who received inpatient treatment at the ICU between March 2020-2021at the Eskişehir Osmangazi University and the Eskişehir Yunus Emre State hospital were examined with due approval from the ethics committee (decision number: 04) of the Eskişehir Osmangazi University (dated: 13/07/2021).

101 of these patients who were discharged with an oxygen concentrator, whose data during the intensive care process could be accessed, and who could be questioned about their symptoms either directly or through relatives after discharge from the hospital were includedin this study.

The data used in the study were obtained from the hospital information system records and patient files. The demographic data of patients, comorbidities, hospitalization vital signs, APACHE 2 scores at the time of admission to the ICU, hemogram, and biochemical parameters were used in the determination of the length of hospital stay and follow-up, and laboratory data such as the values of C-reactive protein, ferritin, and d-dimer were also evaluated. The values that showed the greatest deviation from the physiological values at the time of admission to the ICU were specifically recorded. Macrophage activation syndrome criteria, as recommended by the Ministry of Health, used in the ICUs and the treatments applied were also examined.

Patients discharged from the hospitals were contacted via phone to question about symptoms related to respiratory failure and dyspnea after discharge, the use duration of oxygen concentrator, headache persisting for 1 month and 3 months, fatigue, weakness, breath shortness, loss of taste and smell, chronic cough, whole-body muscle pain, forgetfulness, distraction, sleep disorder symptoms, functional status scale (score 1-7) and the functional status (11).

The functional status was graded as follows:

- Totally dependent
- Needs a high level of help
- Need a moderate level of help
- Need low-level of help
- Can perform their routine jobs with supervision
- Semi-independent
- Fully independent

Statistical Analysis

SPSS version 25.0 (IBM, Armonk, NY, USA) software was applied to conduct all statistical analyses, and the statistical significance threshold was set to p=0.05. The normality of distributions in quantitative variable groups was analyzed with the Shapiro-Wilk test, and the variants were assessed

Table 1. Comparison of patients according tothe stage of dyspnea at discharge

		Dyspnea on discharge		
		No (n=12)	**Yes (n=89)**	**p-value**
Age		61.6±16.4	67.9±12.6	0.227
Gender	Man	9 (75%)	52 (58.4%)	0.431
	Woman	3 (25%)	37 (41.6%)	
Comorbidity	None	6 (50%)	13 (14.6%)	0.011
	There is	6 (50%)	76 (85.4%)	
MAS	None	10 (83.3%)	70 (78.7%)	1.000
	There is	2 (16.7%)	19 (21.3%)	
Pulse		103.33±18.01	95.73±17.21	0.111
Systolic BP		105±14.46	122.03±22.15	0.007
Diastolic BP		58.33±9.37	72.18±13.37	0.001
APACHE 2		18.75±9	18.03±6.72	0.812
Hospital lasting period		12.17±5.36	19.11±19.53	0.034
D-dimer		3033.33±1049.98	4541.8±3856.18	0.089
Ferritin		961.17±652.13	1047.18±604.57	0.570
Lymphocyte		678.33±369	802.36±529.03	0.475
Leukocyte		15050±9773.39	7648.99±4272.09	0.005
Thrombocyte		242666.67±70250.63	218988.76±140088.32	0.111
LDH		487.67±213.62	388.67±135.22	0.062
PaO_2		69.17±14.49	55.74±10.91	0.002
SaO_2		90.67±5.77	85.62±8.07	0.049
CRP		42.25±80.34	146.06±71.22	0.093

MAS: Macrophage activation syndrome, BP: blood pressure, LDH: lactate dehydrogenase, CRP: C-reactive protein

Table 2. Logistic regression analysis of the patient data

	B	**S.E.**	**Wald**	**df**	**p-value**	**Exp(B)**	**95% CI for Exp(B)**	
Leukocyte	–0.001	0	4.819	1	0.028	0.999	0.998	0.999
PaO_2	–0.214	0.091	5.553	1	0.018	0.807	0.676	0.965
Systolic BP	0.197	0.091	4.714	1	0.030	1.217	1.019	1.454

BP: Blood pressure, df: degree of freedom, CI: confidence interval

with the Levene test. Quantitative data were defined as the mean ± standard deviation values irrespective of the parametric/non-parametric status. Nonetheless, depending on whether the parametric assumptions were met (Student's t-test or Mann-Whitney U test); validation was made with comparison tests. Chi-square tests (continuity correction or Fisher's sharpness) were performed to match the distributions of the nominal or ordinal variables between the groups. Multiple regression analysis was performed for the independent variables, and the statistical significance threshold was set to p=0.1.

Results

The average age of the 101 (61 men, 40 women) study patients evaluated was 67 years. Of these, 18 patients did not have any comorbid disease, 83 had common comorbid diseases of diabetes mellitus (n=33), hypertension (n=27), coronary artery disease (n=18), chronic obstructive pulmonary disease and asthma (n=13), congestive heart failure, cancer, atrial fibrillation, component resolved diagnosis, and circumventricular organs. The mean APACHE 2 score calculated for these patients during the intensive care hospitalization was 18, and the mean hospitalization period was 18 days. Respiratory support provided to the patients during hospitalization was in the form of nasal cannula (n=4), simple mask (n=3), mask with reservoir (n=13), high flow nasal oxygen (n=45), non-invasive mechanical ventilation (NIMV) (n=29) and intermittent mandatory ventilation (IMV) (n=7).

All patients included in the study were discharged with an oxygen concentrator support and assigned to two groups based on the presence (n=89) or absence (n=12) of dyspnea at the time of discharge. These two groups were analyzed and compared individually based on age, gender, presence of comorbid diseases, vital signs (such as pulse and blood pressure), APACHE 2 score, laboratory parameters, and the length of stay. In this comparison (shown in Table1), although the mean age and the number of men were higher in the dyspnea group, the differences were not statistically significant.

The comorbidity rate in the dyspnea group was 85.4% and14.6% of the patients did not have any comorbidities (p=0.011). Moreover, the length of hospital stay was19.11±19.53 days in the dyspnea group and 12.17±5.36 days in the non-dyspnea group, indicating that this difference was statistically significant (p=0.034). On the other hand, the levels of d-dimer, ferritin, and C-reactive protein were higher in the dyspnea group, albeit the difference was not statistically significant.

In the data supported by multivariate logistic regression analysis in the independent variables (Table2), the low values of PaO_2 (55.74±10.91) and SaO_2 (85.62±8.07) (p=0.002 and p=0.049) and the high values of systolic and diastolic blood pressure (122.03±22.15 and 72.18±13.37; p=0.007 and p=0.001) in the dyspnea group were found to be significant. In addition, dyspnea symptoms were present at the time of discharge in 6 of the 7 patients who received IMV support, in 26 of the 29 patients who received NIMV support, and in 42 of the 45 patients who received high-frequency oscillation support. Meanwhile, 85 of the 101 patients did not need an oxygen concentrator at the end of the 3rd month and their dyspnea symptoms decreased from 89% to 18%.

In the 1st and 3rd months after discharge, the symptom inquiries were made using the information obtained from the patients who were in a good general condition and from the relatives of the patients who were in a poor health state. The most common symptoms in the 1st month were weakness, fatigue (99%), shortness of breath (89%), headache (37%), forgetfulness (35%), sleep disturbance (33%), cough (24%), muscle pain (22%), and the loss of taste and smell (8%). The frequency of symptoms decreased significantly in the 3rd month, and the most common symptoms that continued were fatigue (28%), forgetfulness (27%), and breath shortness (18%). No such symptoms continued or remained in 50 patients.

Another parameter questioned during the study was the functional status scoring, and the patients were scored in the range of 1-7. While the dependent group (n=75) was scored between 1 and 4 on the functional status scale, the independent group was scored between 5 and 7 (n=28). Although there was no significant difference in age, gender, laboratory parameters, the length of stay, and treatment received between the dependent and independent groups (based on the functional status scale at the 1st month), the significance of male gender and comorbidity was higher in the dependent group. Although the APACHE 2 score was 19.03±6.75 in the functionally dependent group, it was 15.5±7.1 in the independent group. The high APACHE 2 score (p=0.038) detected in the addicted group was found to be statistically significant. In addition, the functional status of oxygen support administered during the ICU admission

was found to be significantly higher in the dependent group (p=0.019). All patients who received the IMV support and 24 of the 29 patients who received the NIMV support at the time of discharge were found to be dependent. In conclusion, according to the functional status scale of 101 patients, 75 of them were dependent and 26 were independent in the 1st month and 20 patients became dependent and 81 patients became independent by the end of the 3rd month. Furthermore, 62 patients in the independent group returned to their fully independent working life mode (Table 3).

Discussion

According to the Centers for Disease Control and Prevention (CDC) data, the incidence of symptoms during the post-COVID period was 5-80%. According to this study, the risk factors were found to be age >50 years, presence of hypertension, female gender, asthma, and obesity (12). In our study, the average age of the patient was 67 years, which was consistent with these data. Moreover, comorbidity and the length of hospital stay were found to be significant in terms of the incidence of dyspnea at the time of discharge in patients followed up at the ICU with the diagnosis of COVID-19. Diagnoses of diabetes mellitus and hypertension were found to be the most common ones among the comorbid diseases. Low PaO_2 and SaO_2 values and the hypertensive course of the patients were also determined as risk factors for the continuation of dyspnea. The length of the dyspnea period in hypertensive patients is believed to be related to the renin–angiotensin

Table 3. Comparison of dependent and independent patients

		Dependant (n=75) FDS=1-4	**Independent (n=26) FDS=5-7**	**p-value**
Age		67.4±12.9	66.7±14.2	0.867
Gender	Man	44 (58.7%)	17 (65.4%)	0.711
	Woman	31 (41.3%)	9 (34.6%)	
Comorbidity	None	13 (17.3%)	6 (23.1%)	0.565
	There is	62 (82.7%)	20 (76.9%)	
MAS	None	60 (80%)	20 (76.9%)	0.958
	There is	15 (20%)	6 (23.1%)	
CRP		148.19±75.71	124.31±61.42	0.161
D-dimer		4402.67±3665.05	4246.92±3921.14	0.532
Ferritin		1002.61±623.41	1136.04±559.2	0.296
Lymphocyte		717.6±394.49	989.62±730.6	0.085
Leukocyte		8351.73±5977.09	9037.69±4829.92	0.253
PaO_2		55.65±10.7	62.19±14.69	0.094
SaO_2		85.51±8.04	88.27±7.61	0.139
Systolic BP		120.65±23.35	118.15±17.97	0.805
Diastolic BP		69.75±14.11	72.81±12.37	0.207
APACHE 2		19.03±6.75	15.5±7.1	**0.038**
Hospital period		18.97±20.72	16.31±9.98	0.354
Oxygen support	Nasal O_2	1 (1.3%)	3 (11.5%)	**0.019**
	Mask	3 (4%)	0 (0%)	
	Mask with reservoir	9 (12%)	4 (15.4%)	
	High flow O_2	31 (41.3%)	14 (53.8%)	
	NIMV	24 (32%)	5 (19.2%)	
	IMV	7 (9.3%)	0 (0%)	

MAS: Macrophage activation syndrome, BP: blood pressure, CRP: C-reactive protein, NIMV: non-invasive mechanical ventilation, IMV: intermittent mandatory ventilation

system. Kreutz et al. (13) indicated the relationship between immune and inflammatory dysregulation and hypertension in patients diagnosed with COVID-19 in their study. Detailed information about lung damage and pathophysiology caused by angiotensin-converting enzyme 2 down regulation and the proinflammatory and profibrotic effects of the renin-angiotensin system on angiotensin type-1 receptors have also been discussed (13). In our study, both the presence of hypertension as comorbidity and the hypertensive follow-up of the patients were found to be risk factors indicative of possible lung damage and the continuation of dyspnea symptoms. Despite this, 85 of the 101 patients did not require an oxygen concentrator at the end of the 3rd month and the dyspnea symptom reduced from 89 to 18% by the end of the 3rd month.

The most common symptoms noted in the 1st month of the prolonged COVID-19 period were weakness, fatigue, and shortness of breath, although these symptoms were completely resolved in 50% of the patients and at least 1 symptom continued in 50% of the patients by the end of the 3rd month. The most common ongoing symptoms were determined to be fatigue and forgetfulness. In a study conducted in Italy, 83% of the 143 patients hospitalized due to COVID-19 continued to show at least 1symptom even after 60 days of discharge on an average (14). Our results were found to be consistent with these past data. In fact, similar results were reported in the study conducted by Mark et al. (15) who examined different age groups of patients with COVID-19, the duration of symptoms, the time to return to a healthy life after discharge, and the relevant risk factors. The presence of post-COVID-19 symptoms was not found to be associated with any laboratory data in CDC data. In addition, there are insufficient studies and data in the literature on this subject. Based on our findings and as per the literature, there are no laboratory parameters yet established to determine the post-COVID symptoms.

Although the usability of the functional status scale has been demonstrated in patients with prolonged COVID symptoms by Felipe et al. (16), it is imperative that the scales used in the ICUs should be able to be easily integrated into clinical follow-up without the need for physical function and additional equipment (11).Therefore, we used a similar scale, as demonstrated in a Brazilian study, to evaluate patients for their functional status. The patients were compared as either dependent or independent. Our results showed that 75 out of 101 patients were still dependent in the 1st month, whereas 81 gained independence by the 3rd month and 62 returned to their work post-COVID. The high APACHE 2 score between the two groups was indicative of statistical significance in the dependent group. The APACHE 2 scoring system provides an assessment by taking into consideration several physiological variables of the body systems, the patient's age, and the chronic health status. An APACHE 2 score >15 signifies that the disease is severe (17). In our study, the APACHE 2 score in the addicted group was found to be 19.03±6.75, which is consistent with past reports. Hence, the oxygen requirement and the mechanical ventilation support provided during the ICU hospitalization were found to be significantly higher in the dependent group relative to that in the independent group. Immobilization, physical reconditioning, and the loss of strength were common in patients receiving MV due to the diagnosis of acute respiratory failure. Long-term mechanical ventilation application can reduce the muscle strength in patients hospitalized in the ICU (18).

Conclusion

The study findings indicated that the most important risk factors for dyspnea during the prolonged COVID-19 period were comorbidity and hypertension. No determinant laboratory parameters were recorded during this period. An inverse correlation was noted between the improvement of prolonged COVID-19 symptoms and the functional status after discharge and between the severity of the disease during the intensive care hospitalization and the oxygen support provided.

Considering the risk factors, comorbidities, and the hospitalization process of the patients, the transition to normal life after discharge can be accelerated with early discharge and more effective rehabilitation in accordance with their functional status. This approach can prevent labor loss and reduce the healthcare expenditure.

Ethics

Ethics Committee Aproval: Eskişehir Osmangazi University (Dated: 13/07/2021,decision number: 04).

Informed Consent: The data used in the study were obtained from the hospital information system records and patient files.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.V.K., İ.K.G., B.Y.Y., Concept: İ.V.K., İ.K.G., B.Y.Y., Design: İ.V.K., İ.K.G., B.Y.Y., Data Collection and Process: İ.V.K., İ.K.G., B.Y.Y., Analysis or Interpretation: İ.V.K., İ.K.G., B.Y.Y., Literature Search: İ.V.K., İ.K.G., B.Y.Y., Writing: İ.V.K., İ.K.G., B.Y.Y.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosures: The authors declared that this study received no financial support.

References

1. Halk Sağlığı Genel Müdürlüğü. Genel Bilgiler, Epidemiyoloji ve Tanı Aralık 2020, Ankara. Available at: https://covid19.saglik.gov.tr/TR-66337/genel-bilgiler-epidemiyoloji-ve-tani.html
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727-33.
3. Callard F, Perego E. How. Why patients made long COVID. Soc Sci Med. 2021;268:113426.
4. COVID-19 rapid guideline: managing the long-term effects of COVID-19 NICE guideline; Published: December 18 2020.
5. Mahase E. COVID-19: what do we know about "long COVID"? BMJ. 2020;370:m2815.
6. King's College London. New research identifies those most at risk from "long COVID. 21 October 2020; 06.12.2020 Available at: http://kcl.ac.uk/news/study identifies-those-most-risk-long-COVID.
7. Long-term effects of COVID-19. Accessed on: 06.12.2020 Available at: http://cdc.gov/coronavirus/2019-ncov/long-term-effects.htm.
8. Barman MP, Rahman T, Bora K, Borgohain C. COVID-19 pandemic and its recovery time of patients in India: A pilot study. Diabetes Metab Syndr. 2020;14:1205-11.
9. Nehme M, Braillard O, Alcoba G, Aebischer Perone S, Courvoisier D, Chappuis F, et al. COVID-19 Symptoms: Longitudinal Evolution and Persistence in Outpatient Settings. Ann Intern Med. 2021;174:723-5.
10. Bohn MK, Lippi G, Horvath A, Sethi S, Koch D, Ferrari M, et al. Molecular, serological, and biochemical diagnosis and monitoring of COVID-19: IFCC task force evaluation of the latest evidence. Clin Chem Lab Med. 2020;58:1037-52.
11. Silva VZMD, Araújo JA Neto, Cipriano G Jr, Pinedo M, Needham DM, Zanni JM, et al. Brazilian version of the Functional Status Score for the ICU: translation and cross-cultural adaptation. Rev Bras Ter Intensiva. 2017;29:34-8.
12. Keypoints I Evaluating and caring for patients with post-COVID conditions CDC. Available at: https://stacks.cdc.gov/view/cdc/107148
13. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, et al. Hypertension, the renin–angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID 19. Cardiovasc Res. 2020;116:1688-99. Erratum in: Cardiovasc Res. 2021;117:2394.
14. Carfì A, Bernabei R, Landi F, For the Gemelli Against COVID. 19 post-acute care study group. Persistent Symptoms Patients After Acute COVID-19. JAMA. 2020;324:603-5.
15. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network - United States, March-June 2020. MMWR Morb Mortal Wkly Rep. 2020;69:993-8.
16. Machado FVC, Meys R, Delbressine JM, Vaes AW, Goërtz YMJ, van Herck M, et al. Construct validity of the post-COVID-19 Functional Status Scale in adult subjects with COVID-19. Health Qual Life Outcomes. 2021;19:40.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Apache II: a severity of disease classification system. Crit Care Med. 1985;13:818-29.
18. Ricks E. Critical illness polyneuropathy and myopathy: a review of evidence and the implications for weaning from mechanical ventilation and rehabilitation. Physiotherapy. 2007;93:151-6.

Turk J Intensive Care 2024;22:296-304
DOI: 10.4274/tybd.galenos.2023.71676

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Meltem Ulus,
Aylin Durmaz Edeer

Strain of Care for Delirium Index: Validity and Reliability

Deliryum Bakım Zorluğu Ölçeği: Geçerlik ve Güvenirlik Çalışması

Received/Geliş Tarihi : 15.01.2023
Accepted/Kabul Tarihi : 13.12.2023

Meltem Ulus
Department of Surgical Nursing, Dokuz Eylul University, Health Sciences Institute, Izmir, Turkey

Aylin Durmaz Edeer
Dokuz Eylül University Faculty Of Nursing, Department Of Surgical Nursing,İzmir, Turkey

Meltem Ulus, (✉),
Department of Surgical Nursing, Dokuz Eylul University, Health Sciences Institute, Izmir, Turkey

E-mail : meltemm.ulus@gmail.com
ORCID ID : orcid.org/0000-0001-9779-8597

ABSTRACT *Objective:* Care burden threatens the physical, psychological, emotional, and functional health of caregivers. Caring for patients with delirium leads to stress, increased emotional load and workload in nurses. The strain of care for delirium index (SCDI) was developed to measure the subjective burden of nurse's experience in the care of patients with delirium. The aim of this study is to examine the Turkish validity and reliability of the "The SCDI".
Material and Methods: This study was conducted in a methodological and cross-sectional type. The sample consisted of 102 nurses working in the intensive care unit for at least 6 months.
Results: The goodness-fit indices obtained in the confirmatory factor analysis were at an acceptable level. In the explanatory factor analysis of the scale, factor loads were found to be between 0.343 and 0.865. Item-to- total correlation coefficients ranged from 0.298 to 0.627 and above 0.20 for each item.
Conclusion: Reliability refers to consistency between independent measurements of the same thing. In this study, Cronbach's alpha coefficient and item-total correlations were used to measure reliability. In this study, the Cronbach's alpha coefficient was 0.89. Therefore, SCDI has been accepted as a highly reliable measurement tool. In the reliability analysis of the original index, the Cronbach's alpha coefficient was found to be 0.88. The Turkish version of the SCDI is a valid and reliable scale to evaluate the care difficulty of nurses caring for patients with delirium.
Keywords: Care burden, critical care, delirium, nursing, reliability and validity

ÖZ *Amaç:* Bakım yükü, bakım verenlerin fiziksel, psikolojik, duygusal ve fonksiyonel sağlığını tehdit eder. Deliryumlu hastalara bakım vermek hemşirelerde strese, duygusal yükün ve iş yükünün artmasına neden olur. Deliryum bakım zorluğu ölçeği, deliryumlu hastaların bakımında hemşire deneyiminin öznel yükünü ölçmek için geliştirilmiştir. Bu çalışmanın amacı "Deliryum Bakım Zorluğu Ölçeği (SCDI)"nin Türkçe geçerliğini ve güvenirliğini incelemektir.
Gereç ve Yöntem: Bu çalışma metodolojik ve kesitsel tipte yapılmıştır. Örneklemi yoğun bakım ünitesinde en az 6 aydır çalışan 102 hemşire oluşturmuştur.
Bulgular: Doğrulayıcı faktör analizinde elde edilen iyilik uyum indeksleri kabul edilebilir düzeydedir. Ölçeğin açıklayıcı faktör analizinde faktör yükleri 0,343-0,865 arasında bulunmuştur. Madde toplam puan korelasyon katsayıları 0,298-0,627 arasında ve her bir madde için 0,20'nin üstünde bulunmuştur.
Sonuç: Güvenilirlik, aynı şeyin bağımsız ölçümleri arasındaki tutarlılığı ifade etmektedir. Bu çalışmada güvenirliği ölçmek için Cronbach's alpha katsayısı ve madde-toplam korelasyonları kullanılmıştır. Çalışmanın Cronbach's alpha katsayısı 0.89'dur. Bu nedenle SCDI oldukça güvenilir bir ölçme aracı olarak kabul edilmiştir. Orijinal indeksin güvenirlik analizinde Cronbach alfa katsayısı 0,88 olarak bulunmuştur. SCDI'nin Türkçe versiyonu deliryumlu hastaya bakım veren hemşirelerin bakım zorluğunu değerlendirmede geçerli ve güvenilir bir ölçektir.
Anahtar Kelimeler: Bakım yükü, yoğun bakım, deliryum, hemşirelik, güvenilirlik ve geçerlik

Introduction

Delirium is an acute brain syndrome in which mental functions are generally reversible, with a sudden, fluctuating course in consciousness, perception, thought, sleep-wake cycle, which disrupts brain functions due to an organic cause, and the brain is widely affected in a short time (1,2).

In a meta-analysis and systematic reviews conducted in different patient groups, it was stated that the incidence of delirium increased by up to 52% (3-5). In the literature, it is stated that delirium causes prolonged mechanical ventilation, intensive care unit (ICU), and hospital stay, increased mortality, and long-term cognitive impairment (6,7). Patients may experience disturbing symptoms of psychosis, such as delusions, hallucinations, and altered mood. Patients with delirium tend to exhibit cognitive and behavioral fluctuations. Caregivers to patients with delirium have great difficulty managing these conditions (8). Studies have shown that delirium causes care difficulties for nurses (9,10).

Caring for patients with delirium leads to stress and increased emotional load and workload in nurses (11). Care burden defines as a multidimensional response to the negative evaluation and perceived stress resulting from the care of the patient. Care burden threatens the physical, psychological, emotional, and functional health of caregivers (12,13). In the literature, there are two studies evaluating the care difficulties of nurses who care for patients with delirium (10,14). The strain of care for delirium index (SCDI) was developed to measure the subjective burden of nurses' experience in the care of patients with delirium.

This study aimed to investigate the Turkish validity and reliability of the "The SCDI" developed to measure the subjective burden of nurses' experience in the care of patients with delirium.

Materials and Methods

This study is a methodological and cross-sectional.

Study Sample

We used the matched sampling method in sample selection. It is recommended that the sample size be 5-10 times the number of items in the scale (15-17). Therefore, the sample size was planned to at least 100 intensive care nurses. The data were collected from the nurses who worked in the ICU of the training and research hospital for at least 6 months between March and May 2022 using a questionnaire collection method. A sample of 102 nurses who agreed to participate in the study.

Data Collection Tools

We collected data with the "introductory information form" and "SCDI".

a. Introductory Information Form: This form includes the descriptive characteristics of nurses, such as gender, age, and working years. This form, developed by the researchers in line with the literature, consists of 8 questions.

b. SCDI: This scale was developed by Milisen et al.(18) The aim of this scale was to determine the difficulties experienced by nurses when providing care to patients with delirium. The scale comprises 20 items and is a four-point Likert scale. The scale consists of 4 sub-dimensions as "hypoalert behavior, fluctuating course and psycho-neurotic behavior, and hyperactive/hyperallert behavior". The total score ranged from 20 to 80, with higher scores indicating greater difficulty in coping with delirium. The four-factor index explains 61.51% of the total variance and the internal consistency Cronbach's alpha reliability coefficient is 0.88 (18).

Data Collection

We applied an introductory information form and an adapted scale to the nurses participating in the study. We applied the scale again after 6 weeks to evaluate its invariance. It took 1 min to answer the scale.

Statistical Analysis

Data Statistical Package for Social Sciences version 22.0 (SPSS, Inc. Chicago, IL, USA) and AMOS version 21. The content validity of the scale was examined with the Polit and Beck Content Validity Index by obtaining expert opinions. (19) Construct validity of the scale; analyzed by exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) (16,20). In the reliability of the scale, item-total correlations were determined, and the internal consistency of the scale and its subdimensions was examined with the Cronbach's alpha reliability coefficient (16,21,22).

Test-retest measurement results showed a normal distribution; the difference between the mean scores obtained from the two measurement results, invariance vs. time, was examined with the "t-test independent groups". The Hotelling T2 test was used to evaluate whether the participants' responses to the scale items were equal (Figure 1).

Ethical Approval

Ethics committee approval was obtained from the Izmir Katip Celebi University non-interventional clinical research

ethics committee (decision number: 0399 and decision date: 21.09.2021), and written institutional permission was obtained from Atatürk Training and Research Hospital. Nurses working in the ICU were informed about the purpose and methods of the study, and verbal and written informed consent was obtained from each participant.

Results

Characteristics of the Participants

The mean age of nurses was found to be 26.69±4.48 years; moreover, 78.4% were female, and 70.6% had undergraduate education. The nurses participating in the research had been working as nurses for a minimum of 6 months and a maximum of 22 years and have been working in the ICU for at least 6 months and a maximum of 16 years (Table 1). Of the participants, 75.5% stated that they received education on delirium.

Validity analysis

1.Examination of Content-Language Validity

Language Validity

First, two native speakers translated the scale from English to Turkish to ensure the language validity of the "SCDI". Second, two experts who were fluent in both the Turkish and English languages and cultures and did not see the English version of the original scale translated the scale from Turkish to English. Third, the English-Turkish and Turkish-English translations were checked, and they were found to be similar. Thus, a Turkish version of the scale was created.

Content Validity

To analyze the content validity, eight specialists, namely, physicians, nurses, and faculty members in the field of cardiovascular surgery and psychiatry, were asked to provide their opinions on the applicability and comprehensibility of the scale items translated into Turkish. The experts evaluated each item on a scale for content validity by scoring between 1 and 4 (1: The item is not suitable, 2: The item should be seriously reviewed, 3: The item should be reviewed, 4: Appropriate).

Scores were given by the experts to the items of the "SCDI" were analyzed using the Polit and Beck Content Validity Index. The content validity index was calculated for both the items and scales. The Content Validity Index of the scale: 1 and Item Content Validity Index: 1. It was determined that there was consensus among the experts. The researchers made necessary corrections to the scale items according to the experts' suggestions. The scale was then evaluated statistically without removing the items.

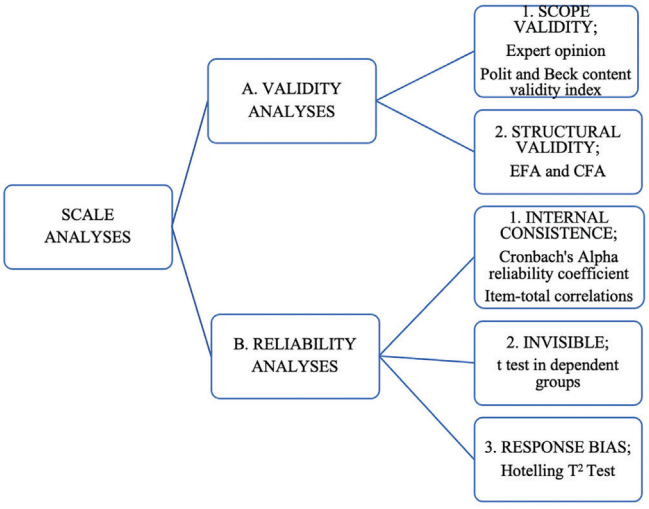

Figure 1. Scale analysis of validity and reliability

Table 1. The descriptive characteristics of intensive care nurses (n=102)

	$\bar{X}$ ± SD	Range
Gender	N (102)	%
Woman	80	78.4
Male	22	21.6
Educational Status		
High school	14	13.7
Associate degree	9	8.8
License	72	70.6
Graduate	7	6.9
ICU		
Cardiovascular surgery	26	25.5
Anesthesia and reanimation in the ICU	33	32.4
Neurosurgery ICU	10	9.8
General surgery ICU	12	11.8
Neurology ICU	5	4.9
Internal medicine ICU	10	9.8
Coronary ICU	6	5.9
Age	26.69±4.48[a]	22-43
Professional working year	3.86±4.04[a]	6 months-22 years
Years working in an ICU	2.98±3.40[a]	6 months-16 years

[a]Values given are mean ± SD, ICU: intensive care unit, SD: standard deviation

Pilot Application

After determining the language and content validity of the scale, a pilot application was conducted. This study was conducted with 20 intensive care nurses, who had the characteristics of the sample and 10% of the sample number (23). Data from the pilot application were excluded from the analysis of this study. In line with the suggestions, the root of the question was changed from "…how is it for you to take care of patients?" to "…how do you deal with patients?" Additionally, the 12th question was edited as "How do you deal with patients who go back and forth between conscious and unconscious periods?" After these revisions, the final scale version was applied to the sample group.

2. Construct Validity

EFA and CFA were performed to assess the construct validity of the scale.

EFA: EFA was conducted to determine the construct validity of the "SCDI" and to determine the factor structure. Therefore, the direct oblivion method, which is an oblique rotation method, was used because there was a relationship between the principal components and factors (24). Sample adequacy was evaluated with Kaiser-Meyer-Olkin (KMO) value in EFA. The KMO value was 0.831, Bartlett's Test χ^2 (190) =943.577 and $p<0.05$ (significant). The SCDI, which consists of 20 items and a structure with 4 sub-dimensions (factors), explained 59.84% of the total variance.

The factor loads of the scale items were between 0.343 and 0.865 (Table 2).

CFA: CFA was performed for the construct validity of the scale. CFA, the results of the fit statistics, and the modification index were examined without making any limitations on the model or adding new connections (Figure 2).

[(χ^2(degree of freedom (df):164, n=102) =313.223, p=0.000, Root Mean Square Error of Approximation (RMSEA)=0.095, Goodness of Fit Index (GFI)=0.775, Adjusted Goodness of Fit Index (AGFI)=0.711, Comparative Fit Index (CFI)=0.820, χ^2/df=1.91] of the scale were obtained. p=0.000 was found (Table 3).

Table 2. Factor loads of scale items

Scale items	Factor loadings
1. How should you manage patients who are withdrawn or who are unusually quiet?	0.606
2. How do you deal with apathetic, disinterested, or unmotivated patients?	0.750
3. How should you manage patients with reduced motor activity?	0.636
4. How do you manage patients who lack knowledge or understanding of their disease/condition?	0.343
5. How should you deal with patients who have difficulty concentrating and are easily distracted?	0.589
6. How do you manage patients who speak slowly or hesitantly?	0.622
7. How should you deal with patients who make little eye contact?	0.573
8. How do you deal with patients who call someone they know by a different name?	0.865
9. How do you deal with patients who are talking to people who are not actually present?	0.860
10. How do you manage patients who engage in repetitive behaviors?	0.679
11. How should you deal with patients with inconsistent speech?	0.640
12. How do you deal with patients who go back and forth between the conscious and unconscious periods?	0.430
13. How should you deal with patients whose sleep/wake cycles are disrupted?	0.597
14. How do you deal with restless or agitated patients?	-0.633
15. How do you deal with patients making noise or shouting?	-0.788
16. How do you manage patients who are irritable?	-0.805
17. How should you manage patients with increased motor activity?	0.504
18. How do you deal with uncooperative or difficult-to-manage patients?	-0.631
19. How do you deal with patients trying to get out of bed inappropriately?	-0.842
20. How do you deal with patients pulling tubes, dressings, and catheters, etc.?	-0.801

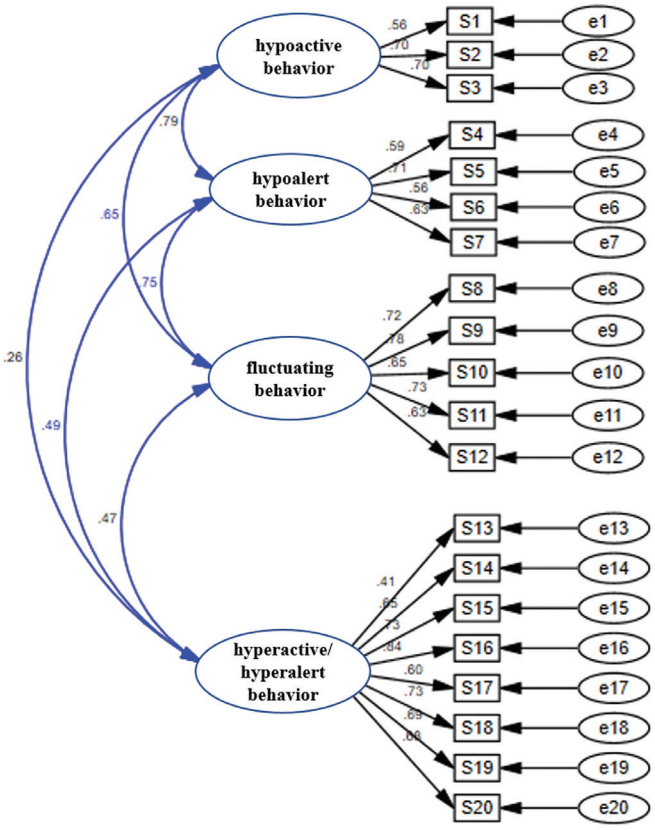

Figure 2. CFA of the delirium difficulty-to-care scale
CFA: Confirmatory factor analysis

Table 3. Examination of CFA compliance with the delirium difficulty-to-care scale

DFA model fit indices	Expected values	SCDI
Minimum fit function chi-square (x^2)	x^2/df <5	1.91
Degree of freedom (df)		
Root Mean Square Error of Approximation (RMSEA)	<0.08	0.095
Root Mean Square Residual (RMR)	<0.08	0.045
Comparative Fit Index (CFI)	>0.90	0.82
Goodness of Fit Index (GFI)	>0.90	0.775
Adjusted Goodness of Fit Index (AGFI)	>0.90	0.711

CFA: Confirmatory factor analysis, SCDI: strain of care for delirium index, DFA: Detrended Fluctuation Analysis

3. Reliability

1. Internal consistency

Cronbach's alpha coefficient

SCDI (Cronbach's alpha coefficient) was found to be α=0.892. Cronbach's alpha coefficients for hypoactive, hypoalert, fluctuating course, and psycho-neurotic and hyperactive/hyperalert behavior subdimensions 0.675, 0.711, 0.828, and 0.863 were found, respectively (Table 4).

The mean SCDI score was 55.50±7.94 and the scale sub-dimension mean score was 7.36±1.58, 9.77±1.91, 13.92±2.73, and 24.45±4.03, respectively (Table 4).

Item-to-total score analysis

The item-to-total score correlation values of SCDI were between 0.298 and 0.627 and above 0.20 for each item. The item-total score correlation coefficients of the subdimensions were between 0.353 and 0.788.

2. Invariance analysis

Test-retest reliability coefficient (Test-retest reliability coefficient): SCDI was administered to 102 nurses working in the ICU twice, with an interval of 6 weeks. It was determined that there was no statistically significant difference between the two measurement results. (p=0.526) (p>0.05) (Table 5).

The test-retest total score average correlation coefficient of the scale was 0.985, and the subscale-total score correlation coefficients were 0.972, 0.968, 0.973, and 0.973, respectively, and were significant (p=0.000). In the first and second applications, a positive, very strong, and significant relationship was found between the scale and the subdimension total scores (Table 5).

3. Response Bias

Scale Response bias; The Hotelling T2 test was used to evaluate whether the participants responded to the scale items in line with the researcher's expectations. Hotelling T2 =234.579 p=0.000, the scale did not have a response bias.

Discussion

Linguistic validity: First, two native speakers of Turkish translated the SCDI from English into Turkish to test the linguistic validity of the SCDI. Second, English by two experts, who were fluent in both Turkish and English languages and cultures but did not see the English version of the original scale, translated it back to English to test

Table 4. Cronbach's alpha reliability coefficient and subdimension analysis results of the delirium difficulty of care scale and its subdimensions

SCDI and its subdimensions	$\overline{X}$ ± SD	SE	median	min.	max.	r	α
1. Subdimension: Hypoactive behavior	7.36±1.58	0.15	7.00	3	11	2.511	0.675
2. Sub-dimension: hypoalert behavior	9.77±1.91	0.18	10.00	4	14	3.662	0.711
3. Subdimension: fluctuating course and psycho -neurotic behavior	13.92±2.73	0.27	14.00	7	20	7.499	0.828
4. Subdimension: hyperactive/hyperalert behavior	24.45±4.03	0.39	24.00	9	32	16.290	0.863
SCDI total	55.50±7.94	0.78	56.00	35	75	63.064	0.892

SCDI: Strain of care for delirium index, SD: standard deviation

Table 5. Test-retest mean scores of SCDI and its subdimensions

	Average score		Analysis Results			
Scale and subdimensions	Test (n=102) $\overline{X}$ ± SD	Retest (n=102) $\overline{X}$ ± SD	t	p[b]	r	p[c]
SCDI	55.50±7.94[a]	55.59±8.06[a]	-0.636	0.526	0.985	0.000
1. Subdimension: Hypoactive behavior	7.36±1.58	7.34±1.58	0.533	0.595	0.972	0.000
2. Sub-dimension: hypoalert behavior	9.77±1.91	9.73±1.90	0.815	0.417	0.968	0.000
3. Subdimension: fluctuating course and psycho -neurotic behavior	13.92±2.73	13.91±2.70	0.155	0.877	0.973	0.000
4. Subdimension: hyperactive/hyperalert behavior	24.45±4.03	24.60±4.13	-1,665	0.990	0.973	0.000
Total	55.50±7.94	55.59±8.06	-0.636	0.526	0.985	0.000

[a] Values are expressed as mean ± SD, [b] p >0.05, [c] p <0.001, SD: standard deviation, SCDI: strain of care for delirium index

whether the Turkish version met the same meaning. In the third stage, the English-Turkish and Turkish-English translations were checked and found to be similar, and the Turkish form of the scale was created. Health professionals familiar with the terminology of the translated scale and who have experience in interviewing and data collection should be involved in the translation process. Translators should also consider the cultural, psychological, and grammatical differences between languages. In the initial and back translation, the emphasis should be on conceptual and cultural equivalence rather than linguistic equivalence (25). The back translation was compared with the original SCDI by the authors of this article, and no changes were made to the Turkish version as it was found to be compatible with the original scale. The language validity criterion of the scale is in line with the literature.

Content validity: Content validity is the extent to which the scale items of the construct to be measured represent the construct to be measured (26,27). For this, the applicability and comprehensibility of the scale items translated into Turkish depend on expert evaluations, and choosing the right number of experts is very important (28). It is recommended to obtain expert opinion on content validity from at least three and at most 10 experts (19). So, expert opinion was obtained from 8 specialist who are experts in delirium and intensive care. The experts' scores for the items of the SCDI were analyzed using the Polit and Beck Content Validity Index. For content validity, the Scale Content Validity Index: One and the Item Content Validity Index: 1. If an expert opinion is obtained from 6-10 people, it is recommended that the item and scale content validity index be 0.80 and above. It was determined that there was consensus among the experts (23). The researchers made necessary corrections to the scale items according to the suggestions of the experts. The pilot study was conducted with 20 intensive care nurses, who had the characteristics of the sample and 10% of the sample number (23). In the pilot study, participants were asked to read the question aloud and give a brief explanation about the meaning of each item. If an item is not easily understood, the respondent's opinion

should be sought regarding how the question could be expressed in another way. In this way, it should be ensured that the substance is understood in the same way by every individual (25). According to the suggestions of the pilot study participants, we changed the roots of the questions and edited the 12th question.

Construct validity: EFA and CFA

In EFA, the researcher attempts to reveal the structure between variables, while CFA is suitable for situations where there are hypotheses about the structure in question based on pre-established or previous research and researchers are interested in testing them. The Bartlett test is used to determine whether the correlation coefficients are significant in EFA (29). The KMO was found to be 0.831, which indicates that the sample size was "perfect" for factor analysis. Also, Bartlett's Test χ^2(df:190) =943.577 and p<0.05 (significant), indicating that the correlation between items was large enough for EFA (17).

In the validity analysis of the scale, the total correlation coefficient was 0.88%. The factor loads of the scale items ranged from 0.343 to 0.865. It is recommended that the factor loads of the items be at least 0.32 (20). Factor loadings explaining the relationship between the factors show that the items are frequently highly correlated (Table 2). It was used to determine the degree of conformity of the subdimensions determined using EFA to the subdimensions created with the help of the hypothesis. It also determines the extent to which the scale items are represented by the determined factors Aytac and Öngen. (30). [(χ^2(df:164, n=102) =313.223, p=0.000, RMSEA=0.095, GFI=0.775, AGFI=0.711, CFI=0.820, χ^2/df:1.91] of the scale were obtained (Table 4). p=0.000 was found.

To achieve harmony between the matrices, the p value should be meaningless. The sample size greatly affects the p-value of the χ^2 statistic and, therefore, results in the rejection of the model unless there are countless samples (31-33). In other words, the χ^2 value is generally significant in practice. Therefore, the value obtained by dividing χ^2 by the df can be considered (31). If χ^2/df is 5 or less, it indicates that the model has an acceptable goodness of fit (31,32). Our χ^2/df value was 1.91 and has a good goodness of fit.

The RMSEA is the square root of the approximate means. It takes values between 0 and 1. If the RMSEA value is less than 0.05, it indicates a perfect fit; conversely, a value less than 0.08 indicates an acceptable fit. If the values are between 0.08 and 0.10, they show moderate agreement, while values below 0.10 are not considered acceptable (31,32,34,35). RMSEA=0.095 and shows moderate agreement. As the Root Mean Square Residual (RMR) value approaches zero, the tested model shows better goodness of fit (31,32,34).

RMR=0.045, the model shows better goodness of fit. CFI gives the difference of the model established from the absence model (null), assuming that there is no relationship between the variables. This is a model that predicts that there is no relationship between the variables. The value of varies between 0 and 1. As the value approaches 1, it is concluded that the degree of goodness of fit increases, and simultaneously, the model with high value CFI exhibits a strong fit (31-34). CFI=0.82, goodness of fit was not as good as expected.

GFI is a goodness-of-fit index that indicates the extent to which the covariance matrix in the sample is measured by the model. The larger the sample size, the higher the GFI value. Although its general value is between 0 and 1, a GFI exceeding 0.90 is considered a good model indicator (32,36). GFI=0.775, goodness of fit was not as good as expected.

The AGFI is the adjusted goodness-of-fit index. This index compensates for the deficiency in the GFI test in high sample volumes. Its value ranges from 0 to 1 and must be above 0.90 (31,32,34,36). AGFI=0.711, and the goodness of fit was not as good as expected.

According to the Detrended Fluctuation Analysis result, χ^2/df was found to have a good and moderate goodness of fit according to the RMSEA and RMR values. However, the goodness of fit of the CFI, GFI, and AGFI values was not as good as expected.

Reliability: Reliability refers to the consistency between independent measurements of the same thing. In this study, Cronbach's alpha coefficient and item-total correlations were used to measure reliability (23). In this study, the Cronbach's alpha coefficient was 0.89. Therefore, SCDI has been accepted as a highly reliable measurement tool (21, 22). In the reliability analysis of the original index, Cronbach's alpha coefficient was found to be 0.88 (18).

Test-retest reliability is the power of a measurement tool to provide consistent results from application to application and to show invariance over time (37). Test-retest reliability is usually estimated by calculating the (38).

The test-retest total score average correlation coefficient of the scale was 0.985, and the subscale-total-score correlation coefficients were 0.972, 0.968, 0.973, and

0.973, respectively, and were significant (p=0.000) (Table 5). A very strong correlation between the two measurement values indicates greater temporal stability or test-retest reliability (38). The first and second application scale total and sub-dimension total point between a positive direction, very strong and significant a relationship to be this shows that the scale has an invariance feature against time and is consistent.

The reliability and validity studies of the scale were conducted only with intensive care nurses.

Conclusions

The SCDI is a valid and reliable tool for examining the burden of care in intensive care nurses caring for patients with delirium. In line with the data obtained from this scale, it is thought that it will help develop research directions to reduce or prevent the difficulty of nurses providing care to patients with delirium. The effectiveness of the interventions planned to reduce the burden of nurses in the care of these patients can be evaluated using this scale. The quality of patient care is expected to increase when the care burden of the nurses caring for patients with delirium is reduced.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the İzmir Katip Celebi University non-interventional clinical research ethics committee (decision number: 0399 and decision date: 21.09.2021), and written institutional permission was obtained from Atatürk Training and Research Hospital.

Informed Consent: Nurses were informed about the study, and written informed consent was obtained.

Acknowledgements

The authors thank the intensive care nurses who agreed to participate in this study. The authors thank specialist nurses, psychiatrists, associate professors, and assistant professors who contributed to the study with their language translation and expert opinions for their contributions to the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.U, Concept: M.U, A.D.E., Design: M.U, A.D.E., Data Collection and Process: M.U., Analysis or Interpretation: M.U, A.D.E., Literature Search: M.U, A.D.E., Writing: M.U, A.D.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they received no financial support for this study.

References

1. Çam O, Engin E. Ruh Hastalıkları Hemşireliği Bakım Sanatı. 1. ed. İstanbul: İstanbul Tıp Kitabevi; 2014.
2. Fan Y, Guo Y, Li Q, Zhu X. A review: nursing of intensive care unit delirium. Journal of Neuroscience Nursing. 2012;44:307-16.
3. Jung P, Puts M, Frankel N, Syed AT, Alam Z, Yeung L, et al. Delirium incidence, risk factors, and treatments in older adults receiving chemotherapy: A systematic review and meta-analysis. Journal of Geriatric Oncology. 2021;12(3):352-60. https://doi.org/10.1016/j.jgo.2020.08.011 .
4. Lee A, Mu J, Joynt G, Chiu C, Lai V, Gin T, et al. Risk prediction models for delirium in the intensive care unit after cardiac surgery: a systematic review and independent external validation. BJA: British Journal of Anaesthesia. 2017;118(3):391-9.
5. Shao S-C, Lai C-C, Chen Y-H, Chen Y-C, Hung M-J, Liao S-C. Prevalence, incidence and mortality of delirium in patients with COVID-19: a systematic review and meta-analysis. Age and ageing. 2021;50(5):1445-53. https://doi.org/10.1093/ageing/afab103 .
6. Kang J, Lee M, Ko H, Kim S, Yun S, Jeong Y, et al. Effect of nonpharmacological interventions for the prevention of delirium in the intensive care unit: a systematic review and meta-analysis. Journal of critical care. 2018;48:372-84. https://doi.org/10.1016/j.jcrc.2018.09.032 .
7. Tilouche N, Hassen MF, Ali HBS, Jaoued O, Gharbi R, El Atrous SS. Delirium in the intensive care unit: incidence, risk factors, and impact on outcome. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2018;22(3):144.
8. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLullich AM, et al. Delirium. Nature Reviews Disease Primers. 2020;6(1):1-26. https://doi.org/10.1038/s41572-020-00223-4.
9. Detroyer E, Dobbels F, Debonnaire D, Irving K, Teodorczuk A, Fick DM, et al. The effect of an interactive delirium e-learning tool on healthcare workers' delirium recognition, knowledge and strain in caring for delirious patients: a pilot pre-test/post-test study. BMC medical education. 2016;16(1):1-10. https://doi.org/10.1186/s12909-016-0537-0 .
10. Tan H, Zhou L, Wu S, Dong Q, Yang L, Xu J, et al. Subjective strain of care experienced by pulmonary and critical care medical nurses when caring for patients with delirium: a cross-sectional study. BMC Health Services Research. 2021;21(1):1-7. https://doi.org/10.1186/s12913-021-06860-z .
11. Sanson G, Khlopenyuk Y, Milocco S, Sartori M, Dreas L, Fabiani A. Delirium after cardiac surgery. Incidence, phenotypes, predisposing and precipitating risk factors, and effects. Heart & Lung. 2018;47(4):408-17. https://doi.org/10.1016/j.hrtlng.2018.04.005 .
12. Işıl Ö, Yaşlı ON. demanslı bireye bakım verenlerde bakım yükü ve yaklaşımlar. T3 rkiye Klinikleri Dergisi. 2016;2(1):74-80.
13. Liu Z, Heffernan C, Tan J. Caregiver burden: A concept analysis. International journal of nursing sciences. 2020;7(4):438-45. https://doi.org/10.1016/j.ijnss.2020.07.012.
14. Schmitt EM, Gallagher J, Albuquerque A, Tabloski P, Lee HJ, Gleason L, et al. Perspectives on the delirium experience and its burden: common themes among older patients, their family caregivers, and nurses. The Gerontologist. 2019;59(2):327-37.
15. Karasar N. Bilimsel Araştırma Yöntemi, Nobel Yayınevi 14. Baskı, Ankara. 2005:81-3.
16. Şencan H. Sosyal ve Davranışsal Ölçümlerde Güvenirlik ve Geçerlilik. 1. ed. Ankara: Seçkin Yayınevi 2005.
17. Tavşancıl E. Ölçme ile ilgili temel kavramlar. Tutumların ölçülmesi ve SPSS ile veri analizi. 3. ed: Nobel Yayın Dağıtım; 2006.
18. Milisen K, Cremers S, Foreman MD, Vandevelde E, Haspeslagh M, De Geest S, et al. The strain of care for Delirium Index: a new instrument to assess nurses' strain in caring for patients with delirium. International Journal of Nursing Studies. 2004;41(7):775-83. https://doi.org/10.1016/j.ijnurstu.2004.03.005.
19. Polit DF, Beck CT. The content validity index: are you sure you know what's being reported? Critique and recommendations. Research in nursing & health. 2006;29(5):489-97.
20. Gürbüz S, Şahin F. Sosyal Bilimlerde Araştırma Yöntemleri Felsefe-Yöntem-Analiz. 4. ed: Seçkin Yayınevi.; 2017.
21. Kalaycı S. SPSS uygulamalı çok değişkenli istatistik teknikleri. 5. ed: Asil Yayın Dağıtım Ltd. Şti.; 2010.
22. Tavşancıl E. Tutumların ölçülmesi ve SPSS ile veri analizi. Ankara: Nobel Yayın Dağıtım; 2010.
23. Polit DF, Beck CT. Essentials of nursing research:Appraising evidence for nursing practice. 7 ed. Philadelphia: Wolters Kluwer Health, Lippincott Williams & Wilkins.; 2010.
24. Tabachnick BG, Fidell LS. Using Multivariate Statistics. Rotation. Oblique Rotation. . 6. ed. USA: Pearson Education Limited; 2014. 491,2,501. p.
25. Çapık C, Gözüm S, Aksayan S. Kültürlerarası ölçek uyarlama aşamaları, dil ve kültür uyarlaması: Güncellenmiş rehber. Florence Nightingale Journal of Nursing. 2018;26(3):199-210. https://doi.org/10.26650/FNJN397481.
26. Yurdugül H. Ölçek geliştirme çalışmalarında kapsam geçerlik indeksinin kullanımı. 2012.
27. Yusoff MSB. ABC of content validation and content validity index calculation. Resource. 2019;11(2):49-54. https://doi.org/10.21315/eimj2019.11.2.6
28. Doğan İ, Doğan N. Ölçek Geliştirme Çalışmalarında Kullanılan İçerik Geçerliliğine Genel Bir Bakış. Turkiye Klinikleri Journal of Biostatistics. 2019;11(2). doi: 10.5336/biyostatik.2019-65953.
29. Uyumaz G, Dirlik EM, Çokluk Ö. AÇIMLAYICI FAKTÖR ANALİZİNDE TEKRAR EDİLEBİLİRLİK: KAVRAM VE UYGULAMA. Abant İzzet Baysal Üniversitesi Eğitim Fakültesi Dergisi. 2016;16(2):659-75.
30. Aytaç M, Öngen B. Doğrulayıcı faktör analizi ile yeni çevresel paradigma ölçeğinin yapı geçerliliğinin incelenmesi. İstatistikçiler Dergisi: İstatistik ve Aktüerya. 2012;5(1):14-22.
31. ÇAPIK C. Geçerlik ve güvenirlik çalışmalarında doğrulayici faktör analizinin kullanimi. Anadolu Hemşirelik ve Sağlık Bilimleri Dergisi. 2014;17(3):196-205.
32. Evci N, Aylar F. Derleme: Ölçek geliştirme çalışmalarında doğrulayıcı faktör analizinin kullanımı. Sosyal Bilimler Dergisi. 2017;4(10):389-412.
33. Hooper D, Coughlan J, Mullen MR. Structural equation modelling: Guidelines for determining model fit. Electronic journal of business research methods. 2008;6(1):pp53-60-pp53-60.
34. Erkorkmaz Ü, Etikan İ, Demir O, Özdamar K, Sanisoğlu SY. Doğrulayıcı faktör analizi ve uyum indeksleri. Turkiye Klinikleri Journal of Medical Sciences. 2013;33(1):210-23.
35. Schubert A-L, Hagemann D, Voss A, Bergmann K. Evaluating the model fit of diffusion models with the root mean square error of approximation. Journal of Mathematical Psychology. 2017;77:29-45. http://dx.doi.org/10.1016/j.jmp.2016.08.004
36. Wang K, Xu Y, Wang C, Tan M, Chen P. A corrected goodness-of-fit index (CGFI) for model evaluation in structural equation modeling. Structural Equation Modeling: A Multidisciplinary Journal. 2020;27(5):735-49. https://www.tandfonline.com/doi/full/10.1080/10705511.2019.1695213 (accessed:13.09.2022).
37. Gözüm S, Aksayan S. Kültürlerarası Ölçek Uyarlaması için Rehber II: Psikometrik Özellikler ve Kültürlerarası Karşılaştırma. Hemşirelikte Araştırma Geliştirme Dergisi 2003(5(1)):3-14.
38. Shou Y, Sellbom M, Chen H-F. Fundamentals of Measurement in Clinical Psychology. Journal: https://doi.org/10.1016/B978-0-12-818697-8.00110-2 .

2024 Hakem Dizini - 2024 Referee Index

Ahmet Coşar
Ali Sait Kavaklı
Aycan Özdemirkan
Aynur Karayol Akın
Banu Terzi
Beliz Bilgili
Çağrı Dinleyici
Demet Aydın Tok
Dilek Memis
Duygu Sönmez Düzkaya
Evren Şentürk
Eylem Kiral
Fatma Ülger
Ferda Şöhret Kahveci
Fethi Gül
Figen Esen
Fulya Kamit
Funda Gök
Funda Timurkaynak
Gül Köknel Talu
Gülbin Aygencel Bıkmaz
Güntülü Şık
Hafize Öksüz
Hülya Başar
Hülya Sungurtekin
Hülya Türkan
Hüseyin İlksen Toprak
İlkay Anaklı
İsmail Demirel
Jale Bengi Çelik
Kubilay Demirağ
Lale Karabıyık
Levent Döşemeci
Mehmet Turan İnal
Mehmet Uyar
Melike Cengiz
Nahit Çakar
Nalan Demir
Namigar Turgut
Nazim Doğan
Necati Gökmen
Nimet Şenoğlu
Özlem Korkmaz Dilmen
Özlem Polat
Pınar Zeyneloğlu
Refiye Akpolat
Seda Banu Akıncı
Serap Yavuz
Simru Tuğrul
Süleyman Ganidağlı
Ünase Büyükkoçak
Yalım Dikmen
Zafer Çukurova