Clinical case

doi: 10.35366/100876

Revista Mexicana de Anestesiología
October-December 2021
Vol. 44. No. 4. pp 300-304

Anesthetic management of a parturient with Marfan syndrome scheduled for cesarean section: case report and review of literature

Manejo anestésico de una parturienta con síndrome de Marfan programada para cesárea: informe de un caso y revisión de la literatura

John N Laurencio-Ambrosio, M.D.,* Carlos J Shiraishi-Zapata, M.D. MS,‡ Howard Lee, M.D.§

How to cite: Laurencio-Ambrosio JN, Shiraishi-Zapata CJ, Lee H. Anesthetic management of a parturient with Marfan syndrome scheduled for cesarean section: case report and review of literature. Rev Mex Anestesiol. 2021; 44 (4): 300-304. https://dx.doi.org/10.35366/100876

ABSTRACT. Introduction: Marfan syndrome is an inherited disorder that affects connective tissue. **Case:** We report the anesthetic management of a parturient with Marfan syndrome scheduled for an elective C-section. Successful use of a combined spinal-epidural technique was used to provide neuraxial anesthesia; however, she presented an unfavorable evolution due to maternal sepsis. Likewise, a literature review of combined spinal-epidural anesthesia for C-sections in Marfan syndrome pregnant women was performed. **Conclusion:** Anesthetic management of parturients affected by Marfan syndrome during the cesarean section can be challenging. Strict blood pressure control during the intraoperative period has cornerstone importance. Likewise, neuraxial techniques have a significant percentage of failure in these patients.

***RESUMEN. Introducción:** El síndrome de Marfan es un desorden hereditario que afecta el tejido conectivo. **Caso:** Reportamos el manejo anestésico de una parturienta con síndrome de Marfan programada para una cesárea electiva. Para administrar anestesia neuroaxial se utilizó un bloqueo combinado espinal-epidural; sin embargo, la paciente presentó una evolución desfavorable debido a sepsis materna. Asimismo, se realizó una revisión de la literatura del uso de esta técnica anestésica para cesárea en gestantes con síndrome de Marfan. **Conclusión:** El manejo anestésico de parturientas afectadas por este síndrome puede ser complicado. El control estricto de la presión arterial durante el intraoperatorio tiene importancia fundamental. Además, las técnicas neuroaxiales tienen un porcentaje significativo de fallo en estas pacientes.*

Keywords:
Pregnant women, Marfan syndrome, anesthesia obstetrical, postoperative complications, shock septic.

Palabras clave:
Mujeres embarazadas, síndrome de Marfan, anestesia obstétrica, complicaciones postoperatorias, choque séptico.

* Staff Anesthesiologist, Department of Anesthesiology. Hospital María Auxiliadora. Lima, Perú.
‡ Staff Anesthesiologist, Service of Surgical Center and Anesthesiology, Hospital II Talara. Professor of the Second Specialization Unit, Facultad de Ciencias de la Salud, Universidad Nacional de Piura. Perú.
§ Assistant Professor. Department of Anesthesiology. Northwestern University. Feinberg School of Medicine. Chicago, Illinois, USA.

Correspondence:
Carlos J Shiraishi-Zapata
Avenida Panamericana
s/n Talara, Piura-Perú.
Phone number: 0051-969825842
E-mail: shiraishi52@hotmail.com
cshiraishiz@unp.edu.pe

Received: 05-11-2020
Accepted: 09-03-2021

Abbreviations:
MFS = Marfan syndrome.
ME = Extracellular matrix.
CARE guidelines = Case report guidelines.
ICD = International Classification of Diseases.
ASA = American Society of Anesthesiologists.
NIBP = Non-invasive blood pressure.
IBP = Invasive blood pressure.
CVC = Central venous catheter.
HR = Heart rate.
PACU = Postanesthesia Care Unit.
RR = Respiratory rate.
ICU = Intensive Care Unit.
APACHE = Acute Physiology, Age, Chronic Health Evaluation.
Hgb = Hemoglobin.
ECG = Electrocardiogram.
WHO = World Health Organization.
SOFA = Sequential (Sepsis-related) Organ Failure Assessment Score.
MAP = Mean arterial pressure.

INTRODUCTION

Marfan syndrome (MFS) is an autosomal dominant disease first described in 1896. It affects the connective tissue and has a specific phenotype characterized by cardiovascular, musculoskeletal and ocular manifestations[1,2]. Prevalence rates range from 1.5 to 17.2 per every 100,000 individuals. Approximately, 1 in 5,000 to 1 in 10,000 live newborns[3]. Most cases are caused by a mutation in the fibrillin-1 gene located on chromosome 15 (15q21.1). Patients with this mutation have wide phenotypic heterogeneity[3]. Fibrillin-1 is a structural protein, that is inserted into the extracellular matrix (ME) as a component of microfibrils; thus, its mutation causes a weakening of the structure of the ME, increased activity of the transforming growth factor-beta and loss of the interactions between ME and the cell[2,3].

A case of cesarean section (CS) performed with combined spinal-epidural anesthesia in an MFS parturient, is reported with the Hospital Ethics Committee's written consent and adheres to CARE Case reports guidelines.

PATIENT INFORMATION

A 24-year-old nulliparous at 37 weeks' gestation, was admitted for an elective cesarean section as she had cephalopelvic disproportion (ICD-10 O33.1) in the absence of uterine dynamics and positive fetal maturity tests. She was diagnosed with MFS and had successfully had two other surgeries including correction of lens subluxation and dilation and curettag for incomplete spontaneous abortion (the type of anesthesia received in these procedures is unknown).

Clinical findings

On date of service, her weight and height were 62 kg and 1.73 m, respectively. She received three cardiology evaluations as shown in *Table 1*. In the first evaluation, a diagnostic echocardiogram was performed (see diagnostic evaluation). She was medically managed with metoprolol 50 mg orally per day. Given her medical history, she was deemed an ASA grade III according to the ASA physical status classification system. A review of her perioperative laboratory studies noted a hematocrit level of 29.8%.

Diagnostic evaluation

A transthoracic echocardiogram was performed seven weeks before surgery which noted an ejection fraction of 69%. It was also significant for aortic root dilation (41.7 mm in diameter) as well as mild aortic insufficiency, and grade I diastolic dysfunction. The pulmonary arterial pressure and pericardium were normal.

Therapeutic intervention

The patient entered the operating room with non-invasive blood pressure (NIBP) of 60/40 mmHg, although the rest of the vital functions were normal. A 500 mL fluid bolus was immediately given (normal saline). A triple lumen 7 French central venous catheter (CVC) was placed for vasopressor and/or inotrope therapy. Additionally, a 20-gauge arterial catheter was placed to monitor the patient's hemodynamics. Norepinephrine (0.05 µg/kg/min) was initiated, with a notable improvement of her hemodynamics (phenylephrine for EV use is unavailable in the country). She was placed in the left lateral decubitus position for skin infiltration with 1% lidocaine without epinephrine in L2-L3 and a combined spinal-epidural anesthesia (CSEA) was placed without difficulty. An initial spinal dose of 5 mg of bupivacaine 0.5% with 20 µg of fentanyl was administered. Finally, a 20 G epidural catheter was threaded into the epidural space. She was immediately repositioned supine and placed in left lateral tilt 15º. Initially, an epidural supplement of 3 mL of 2% lidocaine without adrenaline was administered per catheter to reach the level of T4. During surgery, she was resuscitated with 1,100 mL of crystalloids as well as 1,200 mL of 3.5% haemaccel. The infant was delivered within 3 minutes of incision, with an Apgar score of 8 points at the first and fifth minute. The rest of the surgical procedure was uneventful. The estimated blood loss was 900 mL. She remained on a norepinephrine infusion at 0.05 µg/kg/min throughout the duration of the procedure.

Postoperatively, the norepinephrine was stopped in the Postanesthesia Care Unit (PACU). The epidural catheter was removed after administering 1.5 mg of morphine. Furthermore, a compatible red blood cell concentrate was transfused for anemia correction (post-transfusion hemoglobin of 8.6 g/dL).

The patient was transferred to the Intensive Care Unit (ICU) for monitoring. After 24 hours, she was discharged to the general ward. Cardiology follow-up was unrevealing, and she was discharged home on postoperative day 4.

RESULTS

Six days after the discharge, she was readmitted with fever and abdominal pain. Upon initial assessment, she was found to be hypotensive (70/40 mmHg). On admission, she presented dyspnea, chest pain, and syncope. Restlessness, tachypnea (RR 22 breaths/minute), bilateral rales on pulmonary auscultation, and anuria were evidenced, being hospitalized with the diagnosis of distributive (septic) vs cardiogenic shock and respiratory failure. Hemogram showed a leukocyte count of 11.84 per 10^3 and hemoglobin of 7.32 g/dL. Also, the arterial blood gases test showed metabolic acidosis, respiratory alkalosis, and a serum lactate level greater than 2. Biochemical and coagulation studies were normal. However, echocardiogram was not available at that time. Given her perilous clinical condition, she was intubated and placed on mechanical ventilation. A new CVC was placed for infusion of norepinephrine at an adjustable dose.

After admission to the ICU, dopamine and dobutamine infusions were initiated. Her clinical status continued to deteriorate and subsequently had a cardiac arrest. She received

30 minutes of ACLS, however, ROSC was never achieved. Death was communicated to the relatives and the proceedings for the autopsy of the law were initiated. This examination evidenced multiple organic damage as the basic cause of the patient's death.

DISCUSSION

We performed a peer-reviewed literature search about CSEA management for CS in MFS pregnant women using Medline, SCOPUS, EBSCO, ScienceDirect, and Cochrane database. The search included all studies published without language restriction from the start of databases to June 2020. The search included the following MeSH terms: cesarean section, cesarean delivery, Marfan syndrome, anesthesia. The included reports are shown in *Table 2*.

The anesthetic management of patients with MFS can be challenging due to the lack of literature, dilatation of aortic root and ascending aorta, and presence of dural ectasia (DE) (widening of the spinal canal with the erosion of the vertebral body, widening of the neural foramina, or existence of meningocele)[(4)]. Furthermore, which anesthetic technique is most appropriate for these parturients is still controversial[(5)].

A CSEA was performed for avoiding hemodynamic response to laryngoscopy, orotracheal intubation, and surgery (hypertension, heart rate, myocardial contractility, and aortic wall stress)[(5-7)] since our patient had aortic root dilatation as in previous reports[(4,5,8,9)]. This technique can prevent the possibility of other problems during general anesthesia in MFS patients such as difficult airway, luxation of mandibular, and cervical joints, respiratory restrictive disorder, pneumothorax[(10)], and also the aspiration risk during induction and neonatal depression caused by opioids[(11)]. Likewise, invasive pressure monitoring was performed because of aortic involvement.

In previous reports of CS under CSEA in MFS parturients, it has been suggested to consider this technique in the presence of DE[(4)] or even in patients without symptoms of this condition[(12)]. DE can cause an increase in the capacity and the cerebrospinal fluid of the lumbosacral dural space, causing a restriction of the extension of the intrathecal anesthetic[(4,5,12)], and consequently, a high rate of failures during spinal blocks[(12)]. Likewise, the severity of DE

Table 1: Timeline.

Date	Medical and surgical events	Details
21/07/2012–24/09/2012	Prenatal consultations	The patient received 7 prenatal consultations. No intercurrences
2/08/2012	Cardiology evaluation	The physical examination found a normal NIBP and HR; absence of cyanosis and jugular-vein distention and rhythmic heart sounds with a reinforcement of the second in aortic focus. The electrocardiogram showed sinus rhythm, with a 60º axis and premature ventricular contractions alternated with normal beats
17/08/2012	Transthoracic color Doppler echocardiography	Aortic dilation was evident from the root to the ascending portion. See details in diagnostic evaluation part
15/09/2012	Risk assessment	Class II of the Goldman index was assigned, and recommendations were made for the intraoperative period: avoid adrenergic and overhydration, provide antihypertensive measures, and conditional use of amiodarone for treating extrasystoles
25/09/2012	Medical board	The patient was scheduled for elective surgery with the following suggestions: continue with cardiological indications, prepare the availability of compatible red blood cell concentrate and ICU accommodation for postoperative monitoring
26/09/2012	Cardiology evaluation	The Goldman classification and indications of the previous consultation were identical because the echocardiogram findings did not evidence risk at cardiac function
29/09/2012	Color Doppler ultrasound	A single pregnancy of 33.5 weeks was found by fetal biometrics, normal Doppler flows (umbilical and middle cerebral arteries), and a small fetus for gestational age
10/10/2012	Preoperative anesthesia evaluation	Airway evaluation: permeable, complete dentition, class II of modified Mallampati, central trachea, thyromental distance > 6 cm, interincisor distance > 5 cm
11/10/2012	Cesarean section	She was in PACU for 3 hours, then went to ICU for monitoring and management. Four doses of cefazolin 2 g EV were completed every 6 hours and then the therapy was discontinued
12/10/2012	ICU discharge	She was hospitalized in general ward
15/07/2012	Hospital discharge	She received medical indications but there were no appointment dates for Cardiology and Gynecology offices at medical record
21/10/2012	Reentering by the Emergency Service	She was admitted to trauma shock unit with a diagnosis of distributive (septic) vs cardiogenic shock
22/10/2012	Readmission to ICU	The dead of the patient occurred

NIBP = non-invasive blood pressure; HR = heart rate; ICU = Intensive Care Unit; PACU = Postanesthesia Care Unit.

Table 2: Case reports and case series of cesarean section in MFS parturients performed with CSEA.

Author	Dose and level	Presence of MFS comorbidities	Result	Observations
Ben Letaifa	CSEA at L3-L4 interspace. SD: hyperbaric Bup 5 mg + fentanyl 10 µg + morphine 150 µg. ED: (after 20 min of SD administration) lidocaine 2% 5 mL + fentanyl 10 µg (3 boluses with an interval of 5 min per catheter)	Presence of aortic dissection with MV dysfunction	Suitable blockage higher than T4	Preload with ringer lactate 500 mL. EV infusion of ephedrine 60 mg. SP: 100-150 mmHg. DP: 60-90 mmHg. HR: 100-120 bpm
Saeki	CSEA at T12-L1 level. ED: none. SD: 2.2 mL 0.5% isobaric Bup	MV regurgitation, aortic dissection	Suitable blockage at T6 level	Aortic dissection managed with medical treatment
Baghirzada	**Case 1:** epidural catheter at L3-L4. Spinal puncture at L4-L5 interspace. SD: 0.75% hyperbaric Bup 9 mg. ED: Bup 0.5% 150 mg **Case 2:** epidural catheter at L2-L3 level. SD: 0.75% hyperbaric Bup 13.5 mg + fentanyl 10 µg + morphine 100 µg	**Case 1:** dilated aortic root (42 mm), MV prolapse, bicuspid AV, significant DE (lumbar dural sac area of 4.71 cm^2), cervicothoracic scoliosis **Case 2:** moderate DE (lumbar dural sac area of 3.61 cm^2), dilated aortic root (45 mm)	**Case 1:** suitable block (ED anesthetic titrated during 15 min for reaching T4 level) **Case 2:** suitable block (bilateral T5 sensory level obtained after 15 min, catheter not used for anesthesia)	**Case 1:** used NCOM. Baseline SP was maintained with phenylephrine EV boluses of 0.1 mg. Aortic root repairing surgery five days after CS **Case 2:** used NCOM
Clayton	Reported 7 cases managed with CSEA. Inadequate blocks received: SD: 0.5% hyperbaric Bup 2.8 mL (mean initial dose) (range 1.5-4 mL) + opioids	—	5 blocks were inadequate: 4 of the 5 CSEA parturients required additional measures despite having received ED	Additional measures: 1 patient received general anesthesia, 1 repeated spinal, 2 EV opiates
Heck (only CSEA cases)	**Case 1:** ED: none. SD: Bup 17.5 mg + DM 300 µg **Case 2:** ED: 0.5% L-Bup 10 mL. SD: Bup 10 mg + DM 300 µg **Case 3:** SD: Bup 7.5 mg. ED: 0.5% Bup 5 mL **Case 4:** SD: Bup 12.5 mg + DM 300 µg. ED: 2% lidocaine 5 mL + 0.5% L-Bup 10 mL **Case 5:** SD: Bup 14 mg + DM 300 µg. ED: none **Case 6:** SD: Bup 17 mg + DM 300 µg. ED: 0.5% L-Bup 23 mL **Case 7:** SD: Bup 14 mg + DM 300 µg. ED: 0.5% L-Bup 10 mL + 2% lidocaine (plus adrenaline/bicarbonate) 10 mL	**Case 1:** aortic dilatation (42 mm) **Case 5:** aortic dilatation (59 mm)	**Case 1-2:** adequate blocks **Cases 3-7:** inadequate blocks	**Case 4:** converted to general anesthesia **Case 7:** repeated spinal anesthesia (0.5% Bup 1 mL) **Cases 3 and 5-7:** supplementary analgesia with alfentanil **Cases 5-7:** received nitrous oxide
Sakurai	ED (T12-L1 interspace): 10 mL normal saline + 2% lidocaine 10 mL per catheter (twice). SD (L3-L4 interspace): 0.5% hyperbaric Bup 11 mg + fentanyl 10 µg	Aortic root dilatation (39 mm), DE, scoliosis	Adequate sensory block at T11-T6 (beginning and end of surgery, respectively)	4 mg ephedrine for one episode of hypotension. Hypesthesia and severe postdural puncture headache after CS
Yang	SD: 0.5% hyperbaric Bup 8 mg + 10 µg fentanyl. ED: 2% lidocaine 8 mL + 0.75% ropivacaine 8 mL per catheter (titrated over 20 min)	Aortic regurgitation (repaired aortic root aneurysm during childhood)	Adequate sensory block at T4 level	SP above 100 mmHg (invasive) maintained with ephedrine 4 mg EV (twice)
Coffman	SD: 0.75% Bup 0.5 mL + fentanyl 15 µg + morphine 100 µg (L3-L4 interspace). ED: 2% lidocaine + 1:200,000 epinephrine 5 mL (4 doses) in 10 min (1st catheter). 2-chloroprocaine 5 mL (4 doses) in 10 min (2nd catheter, L2-L3 interspace)	Aortic root replacement caused by aortic dissection one year before CS	Failed block. converted to general anesthesia. CS performed in lateral decubitus position	Monitored invasive pressure. Phenylephrine EV infusion (25-50 µg/min) + 20 µg of epinephrine (two episodes of hypotension)
Naud	Doses provided in CSEA not reported	Dilated aortic root (49 mm), DE	CS without complications. Patient was delivered in lateral decubitus position	Valve-sparing aortic root repair on 5^{th} day after CS

MFS = Marfan syndrome; CSEA = combined spinal-epidural anesthesia; Bup = bupivacaine; min = minute; L-Bup = levobupivacaine; SD = subarachnoid dose; ED = epidural dose; MV = mitral valve; EV = endovenous; SP = systolic pressure; DP = diastolic pressure; HR = heart rate; DE = dural ectasia; AV = aortic valve; NCOM = noninvasive cardiac output monitor; CO = cardiac output; CS = cesarean section; DM = diamorphine.
Source: built by authors with references[4-10,12,13].

may be related to the extent of anesthetics administered intrathecally[5]. The epidural space in patients affected with DE may also have an increased size along with the dural sac, thus requiring a greater volume of a local anesthetic to achieve an adequate level[4].

There are several reports of failures of neuraxial techniques even though CSEA or high anesthetic doses have been administered to compensate for the DE alterations[8,12]. The radiological appearance of the lumbar spine (including the dural sac) may not correlate with the clinical response to neuraxial anesthesia[8,13]. Also, DE gradually worsens with age, so a prior adequate spinal block does not ensure the success of future neuraxial blocks (including CSEA)[5]. Although our patient had no clinical features of DE, a magnetic resonance imaging of the lumbar spine was not performed to rule it out completely.

Based on the above, it should take in mind that neuraxial techniques have a significant percentage of failure in these patients and that strict blood pressure control, avoiding hypertension and hypotension, during the intraoperative period has cornerstone importance.

Our patient had a presumption of infection and a SOFA (Sequential [sepsis-related] Organ Failure Assessment Score) score greater than 2 points (anuria, mean arterial pressure [MAP] less than 70 mmHg, Glasgow score of 13 points) during hospital readmission, which in addition to the need for vasopressors to maintain MAP greater than 65 mmHg and a lactate value higher than 2 mmol/L, allows recognizing a diagnosis of septic shock according to current criteria[14], which was confirmed by necropsy. Indeed, the recognition of maternal sepsis is problematic because gestational physiological changes overlap with the hemodynamic changes of the initial picture of sepsis (for example, the leukocyte elevation that is a normal finding in pregnancy and the expanded plasma volume that permits compensating for longer before a rapid deterioration)[15]. Therefore, a high degree of suspicion including a detailed history and examination is important for the early recognition of maternal sepsis[15]. Along with this, we must admit that, in this case, early follow-up by the outpatient office could have allowed recognizing a scenario compatible with sepsis.

Finally, current guidelines from the Surviving Sepsis Campaign recommend fluid resuscitation with crystalloids over colloids. They also advised volume replacement with albumin in case of the need for large amounts of crystalloids due to failure to achieve predefined hemodynamic endpoints[16]. Caution against the use of colloids in the case of dextrans and gelatins was the result of limited safety evidence. However, hydroxyethyl starch solutions were associated with kidney injury and increased mortality in critically ill patients[17]. In this case, a gelatin solution was used due to contribute maintaining an adequate mean arterial pressure until the arrival of the red blood cell concentrate.

Disclosure of funding received for the work: None.
Conflict of interest: None.

REFERENCES

1. Bitterman AD, Sponseller PD. Marfan syndrome: a clinical update. J Am Acad Orthop Surg. 2017;25:603-609.
2. Meester JAN, Verstraeten A, Schepers D, Alaerts M, Van Laer L, Loeys BL. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. Ann Cardiothorac Surg. 2017;6:582-594.
3. Kumar A, Agarwal S. Marfan syndrome: an eyesight of syndrome. Meta Gene. 2014;2:96-105.
4. Baghirzada L, Krings T, Carvalho JCA. Regional anesthesia in Marfan syndrome, not all dural ectasias are the same: a report of two cases. Can J Anaesth. 2012;59:1052-1057.
5. Sakurai A, Miwa T, Miyamoto Y, Mizuno Y, Ka K. Inadequate spinal anesthesia in a patient with marfan syndrome and dural ectasia. A A Case Rep. 2014;2:17-19.
6. Ben Letaifa D, Slama A, Methamem M, Ben Jazia K, Jegham H. Anesthesia for cesarean section in a Marfan patient with complicated aortic dissection. Ann Fr Anesth Reanim. 2002;21:672-675.
7. Coffman JC, Legg RL, Coffman CF, Moran KR. Lateral position for cesarean delivery because of severe aortocaval compression in a patient with Marfan syndrome: a case report. A A Case Rep. 2017;8:93-95.
8. Heck A, Clayton R, Robinson C. Dural ectasia in Marfan syndrome. Int J Obstet Anesth. 2014;23:287-288.
9. Naud K, Horne G, Van den Hof M. A woman with marfan syndrome in pregnancy: managing high vascular risk with multidisciplinary care. J Obstet Gynaecol Can. 2015;37:724-727.
10. Saeki N, Taguchi S, Kawamoto M. Successful management of a patient with Marfan syndrome complicated with acute aortic dissection using landiolol during Cesarean section. J Anesth. 2010;24:277-279.
11. Jayaram A, Carp HM, Davis L, Jacobson SL. Pregnancy complicated by aortic dissection: caesarean delivery during extradural anaesthesia. Br J Anaesth. 1995;75:358-360.
12. Yang HJ, Baek IC, Park SM, Chun DH. Inadequate spinal anesthesia in a parturient with Marfan's syndrome due to dural ectasia. Korean J Anesthesiol. 2014;67:S104-S105.
13. Clayton R, Robinson C. Inadequate neuraxial anaesthesia in Marfan's syndrome: 8AP5-2. Eur J Anaesthesiol. 2013;30:129.
14. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315:801-810.
15. Burlinson CEG, Sirounis D, Walley KR, Chau A. Sepsis in pregnancy and the puerperium. Int J Obstet Anesth. 2018;36:96-107.
16. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304-377.
17. Martin GS, Bassett P. Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: a systematic review and meta-analysis. J Crit Care. 2019;50:144-154.