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Interaction of basic diseases and low red blood cell count as critical murderer of wound infection after osteosarcoma resection

Wound infection after osteosarcoma resection

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Abstract

Background: Surgical wound infection is one of the common complications in patients after osteosarcoma resection. It is imperative to grasp the risk factors comprehensively. Therefore, this study aimed to explore the risk factors of wound infection and deeply analyze the correlation between risk factors and wound infection.

Methods: The study subjects were 101 patients who underwent osteosarcoma resection between April 2018 and August 2021. The diagnosis of postoperative wound infection was confirmed by postoperative observation of the incision, ultrasound imaging, and pathogenic examination. This study included a series of potential factors, mainly laboratory examination indicators and patients' general information. The statistical methods had Pearson Chi-square test, Spearman-rho correlation test, multifactorial linear regression model, logistic regression analysis, and receiver operating characteristic (ROC) curve.

Results: Pearson Chi-square test and Spearman correlation test showed that red blood cell (RBC) count (P = .033) and basic diseases (P = .020) were significantly correlated with a surgical wound infection after osteosarcoma resection. Logistic regression analysis manifested that basic disease (OR = 0.121, 95% CI: 0.015-0.960, P = .046) and RBC (OR = 0.296, 95% CI: 0.093-0.944, P = .040) have a clear correlation with whether the patients have surgical wound infection after osteosarcoma resection. And the interaction of basic diseases and RBC could diagnose the surgical wound infection sensitively and accurately (AUC = 0.700, P = .014, 95% CI = 0.564-0.836) via the ROC analysis.

Conclusion: Patients with basic diseases and low RBC were risk factors for surgical wound infection after osteosarcoma resection.

Abbreviations: 95% CIs = 95% confidence intervals, AUC = area under the curve, HB = hemoglobin concentration, LOS = length of hospital stay, LY = lymphocyte count, NEUT = neutrophil count, ORs = odds ratios, PLT = platelet count, RBC = red blood cell count, ROC = receiver operating characteristic, VIF = variance inflation factor, WBC = white blood cell count.

Keywords: basic diseases, interaction, osteosarcoma resection, red blood cell, surgical wound infection

1. Introduction

Osteosarcoma resection can correct bone dislocation, relieve tumor mass and replace necrotic joints. The curative effect is exact, and the effect is direct, which is widely recognized by both doctors and patients. However, osteosarcoma resection has the characteristics of: first, long operation time, long wound exposure time, considerable area trauma, tissue integrity, and easy infection[1]; second, in addition to the patient's original major trauma, tumor, primary diseases resulting in the decline of the overall immune capacity of the body. These make osteosarcoma resection patients prone to different degrees of wound infection after surgery. Surgical wound infection is one of the common complications in patients after osteosarcoma resection.[2,3] When the incision site infection is not timely prevented and treated, it will lead to difficult incision healing, seriously affecting the therapeutic effect of surgery, and may cause a severe infection of various organs and endanger the life safety of patients.[4–6]

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The Ethics Committee approved this study of Hangzhou Fuyang District First People's Hospital and The Fourth Hospital of Hebei Medical University. Written informed consent was obtained from all patients.

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Diabetes, cardiovascular disease, cerebrovascular disease, and pulmonary illness are primary preoperative disorders that are thought to be contributors to postoperative problems in various procedures.[7–9] These primary diseases affect the occurrence of postoperative complications in surgical patients through intraoperative anesthesia, surgical tolerance, and postoperative recovery.

Red blood cells (RBCs) are the most common cell type in the human body. Its primary physiological function is to exchange oxygen and carbon dioxide through the cells' hemoglobin and transport oxygen to various organ tissues throughout the body.[10] Several studies have shown that the imbalance of erythropoiesis and destruction contributes to developing postoperative complications.

Researchers believe the orthopedic surgical infection is a complication caused by multiple factors, such as the patient's body quality.[11] However, this factor is complex and diverse, which causes some obstacles to the early prevention of orthopedic surgical wound infection. As such, it is essential to comprehensively grasp the risk factors of wound infection after fracture surgery, find the population, and take targeted intervention measures. In this study, the risk factors for wound infection following osteosarcoma resection were further investigated. The relationships between significant illnesses, red blood cell count (RBC), and wound infection were carefully examined. We examined the study data to lower the incidence of wound infection following osteosarcoma excision and identify the population of wound infection. We provided a scientific basis for managing and preventing wound infection after osteosarcoma resection.

2. Methods

2.1. Ethics and informed consent

The Ethics Committee approved this study of Hangzhou Fuyang District First People's Hospital and Fourth hospital of Hebei medical university. Paper informed consent was obtained from all patients.

2.2. Study subjects

The study subjects were 101 patients who underwent osteosarcoma resection between April 2018 and August 2019. The inclusion criteria are: 18-80 years old, undergoing osteosarcoma resection, and patients without surgical history will be screened for inclusion criteria. Exclusion criteria included: age < 18 or > 80 years, patients with poor cardiac function, pulmonary function, and liver and kidney function who could not tolerate surgery, patients with open fractures requiring emergency osteosarcoma resection, and patients with preoperative surgical site infection.

2.3. Characteristics

This study included a series of potential factors related to postoperative wound infection, including laboratory examination indicators and patients' general information. Laboratory parameters included: white blood cell count (WBC, reference value: 4.0109-10.0109/L), neutrophil count (NEUT, reference value: 1.2109-6.8109/L), lymphocyte count (LY, reference value: 0.8109-4.0109/L), red blood cell count (RBC, reference value: 3.5109-5.5109/L), hemoglobin concentration (HB, reference value: 120-160 g/L), platelet count (PLT, reference value: 100.0109-300.0109/L). The general information of patients includes sex (male vs. female), age (≤65 years old vs. >65 years old), and whether there is a concomitant basic disease (yes vs. no).

All participants underwent clean orthopedic prosthesis implantation and vertebroplasty. The diagnosis of postoperative wound infection was confirmed by postoperative observation of the incision, ultrasound imaging, and pathogenic examination. A comprehensive assessment of surgical wound infections was made.

2.4. Statistics

Data statistics are presented as sample size and percentage. Pearson Chi-square test was used to analyze the relationship between whether patients developed wound infection after surgery and related preoperative factors. Correlation analysis was performed using the Spearman-rho correlation test to examine the correlation between the two further. All preoperative correlates were added to a multifactorial linear regression model to determine the variance inflation factor (VIF). This allowed us to gauge the degree of multicollinearity. Univariate and multivariate logistic regression analyses were used to calculate odds ratios (ORs) for each variable based on their statistical results. We evaluated our study by examining how preoperative comorbidities and RBC interacted to affect the likelihood of wound infection following osteosarcoma excision. The "a by b" interaction was used in multivariate logistic regression analysis to investigate the interaction between "presence or absence of basic diseases" and "RBCs" to determine how the presence or absence of primary diseases and the interaction of RBCs affect the occurrence of wound infection following osteosarcoma resection. Afterward, we divided the study population into four categories according to the statistical results of the interaction between the two, with the criteria of "presence or absence of basic disease" and "RBC," and named this feature "presence or absence of basic disease by RBC." Binary logistic regression was again used for correlation analysis. Finally, we constructed receiver operating characteristic (ROC) curves. We applied the area under the curve (AUC) to assess the accuracy and sensitivity of each factor in diagnosing the degree of orthopedic surgical wound infection.

All statistical analyses were performed using SPSS software (version 24.0; IBM Corporation, New York, USA). $P < .05$ was considered statistically significant.

3. Results

3.1. Pearson Chi-square test

The basic data statistics of blood indicators and wound infection after osteosarcoma resection are described in Figure 1. Pearson Chi-square test results summarized the relationship

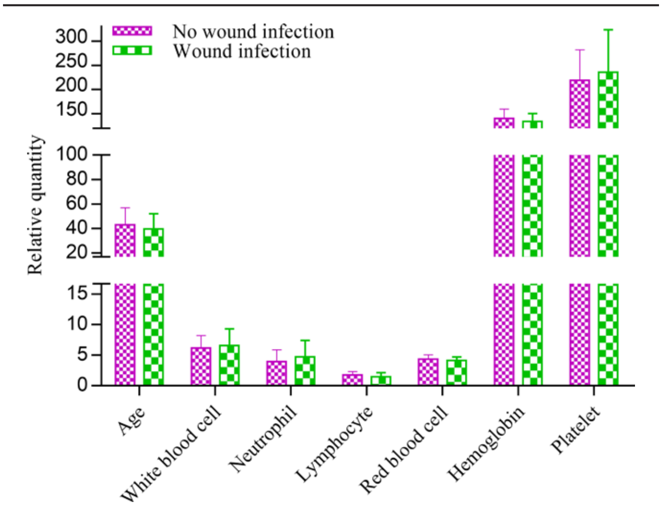

Figure 1. The primary data statistics of blood indicators and wound infection after osteosarcoma resection.

between the relevant parameters of patients and the occurrence of wound infection after osteosarcoma resection. Among them, RBC (*P* = .033) and basic diseases (*P* = .020) were significantly correlated with a postoperative wound infection after osteosarcoma resection. However, there was no significant correlation between sex (*P* = .463), age (*P* = .649), WBC (*P* = .973), NEUT (*P* = .204), LY (*P* = .303), HB (*P* = .164) and PLT (*P* = .192) and postoperative wound infection after osteosarcoma resection (Table 1).

3.2. Spearman correlation test

To further confirm whether various potential characteristics of patients have an important impact on the occurrence of wound infection after osteosarcoma resection, we applied the Spearman correlation test for further correlation analysis. Spearman correlation coefficient showed that basic diseases (ρ = -0.232, *P* = .020) and RBC (ρ = -0.213, *P* = .033) were significantly correlated with postoperative wound infection after osteosarcoma resection. However, there was no significant correlation between other relevant parameters and postoperative wound infection after osteosarcoma resection (Table 2).

3.3. Multiple linear regression analysis

Multiple linear regression analysis of the relationship between characteristics and wound infection showed that the primary disease (β = -0.224, *P* = .037, VIF = 1.179) has a clear correlation with whether the patients have surgical wound infection after osteosarcoma resection. However, there was no significant correlation between other relevant parameters and postoperative wound infection after osteosarcoma resection (Table 3).

3.4. Univariate logistic regression analysis

Furthermore, ORs and 95% confidence intervals (CIs) were used in our study to identify further the risk factors and risk groups for postoperative wound infection following osteosarcoma resection. Binary logistic regression (including univariate and multivariate logistic regression) was used to determine the association between postoperative wound infection and potential factors. Table 4 describes the ORs and 95% CIs of the study subjects at the univariate level using univariate logistic regression and concludes that the basic disease (OR = 0.121, 95% CI: 0.015-0.960, *P* = .046) and RBC (OR = 0.296, 95% CI: 0.093-0.944, *P* = .040) have a clear correlation with whether the patients have surgical wound infection after osteosarcoma resection (Table 4).

3.5. Multivariate logistic regression and interaction analysis

Table 5 applied multivariate logistic regression to describe the OR and 95% CI of the study subjects at the multivariate level. In terms of multivariate logistic regression level, basic diseases (OR = 0.161, 95% CI: 0.19-1.341, *P* = .091), and RBC (OR = 0.427, 95% CI: 0.128-1.419, *P* = .162) were not significantly associated with the occurrence of wound infection after osteosarcoma resection. After studying them by binary logistic regression, we found that the interaction between basic disease and RBC significantly affected wound infection after osteosarcoma resection (OR = 0.421, 95% CI: 0.201-0.883, *P* = .022, Table 5).

We divided all study subjects into four categories with primary diseases and RBC and then performed binary logistic regression analysis again. After osteosarcoma excision, it was discovered that study participants with primary illnesses and low RBCs had a considerably higher risk of wound infection than those without such conditions (OR = 10.000, 95% CI: 1.193-83.837, *P* = .034) (Table 6).

Table 1

Relevant characteristics of patients and wound infection.

Parameters			Wound infection		*P*
			No (%)	Yes (%)	
Sex	Male	98	83 (82.2%)	15 (14.9%)	.463
	Female	3	3 (3.0%)	0 (0.0%)	
Age	<65	91	77 (76.2%)	14 (13.9%)	.649
	≥65	10	9 (8.9%)	1 (1.0%)	
Basic disease	Yes	68	54 (53.5%)	14 (13.9%)	.020*
	No	33	32 (31.7%)	1 (1.0%)	
WBC	Low	61	52 (51.5%)	9 (8.9%)	.973
	High	40	34 (33.7%)	6 (5.9%)	
Neutrophil	Low	62	55 (54.5%)	7 (6.9%)	.204
	High	39	31 (30.7%)	8 (7.9%)	
Lymphocyte	Low	55	45 (44.6%)	10 (9.9%)	.303
	High	46	41 (40.6%)	5 (5.0%)	
RBC	Low	42	32 (31.7%)	10 (9.9%)	.033*
	High	59	54 (53.5%)	5 (5.0%)	
Hemoglobin	Low	44	35 (34.7%)	9 (8.9%)	.164
	High	57	51 (50.5%)	6 (5.9%)	
Platelet	Low	56	50 (49.5%)	6 (5.9%)	.192
	High	45	36 (35.6%)	9 (8.9%)	

Pearson's Chi-squared test was used.
RBC = red blood cell, WBC = white blood cell.
*$P < .05$.

Table 2

The relationship between characteristics of patients and wound infection.

Characteristics	Wound infection	
	ρ	*P*
Sex	−0.073	.468
Age	−0.045	.653
Basic disease	−0.232	.020*
WBC	0.003	.973
Neutrophil	0.126	.208
Lymphocyte	−0.102	.308
RBC	−0.213	.033*
Hemoglobin	−0.138	.167
Platelet	0.130	.196

Spearman correlation test was used.
RBC = red blood cell, WBC = white blood cell.
*$P < .05$.

Table 3

Association between characteristics and wound infection via Multiple linear regression analysis.

Characteristics	Wound infection		
	β	*P*	VIF
Sex	−0.018	.864	1.177
Age	−0.138	.267	1.596
Basic disease	−0.224	.037*	1.179
WBC	−0.794	.453	116.878
Neutrophil	0.817	.446	119.855
Lymphocyte	0.055	.879	13.455
RBC	−0.057	.787	4.704
Hemoglobin	−0.045	.824	4.313
Platelet	0.149	.186	1.320

β = parameter estimate, WBC = white blood cell, RBC = red blood cell, VIF = variance inflation factor.
*$P < .05$.

Table 4

Correlative parameters' effect on wound infection based on univariate logistic proportional regression analysis.

Parameters			Wound infection		
			OR	95% CI	P
Sex	Male	98	1		.999
	Female	3	0.000	0.000–0.000	
Age	<65	91	1		.652
	≥65	10	0.611	0.072–5.210	
Basic disease	Yes	68	1		.046*
	No	33	0.121	0.015–0.960	
WBC	Low	61	1		.973
	High	40	1.020	0.333–3.124	
Neutrophil	Low	62	1		.210
	High	39	2.028	0.671–6.127	
Lymphocyte	Low	55	1		.308
	High	46	0.549	0.173–1.740	
RBC	Low	42	1		.040*
	High	59	0.296	0.093–0.944	
Hemoglobin	Low	44	1		.171
	High	57	0.458	0.149–1.401	
Platelet	Low	56	1		.198
	High	45	2.083	0.681–6.374	

OR = odds ratio, 95% CI = 95% confidence interval, WBC = white blood cell, RBC = red blood cell.
*$P < .05$.

Table 5

The characteristics and their effect on wound infection based on multivariate Logistic proportional regression analysis.

Characteristics	Wound infection		
	OR	95% CI	P
Basic disease	0.161	0.019–1.341	.091
RBC	0.427	0.128–1.419	.165
Basic disease*RBC	0.421	0.201–0.883	.022*

OR = odds ratio, 95% CI = 95% confidence interval, RBC = red blood cell.
*$P < .05$.

Table 6

The interaction of basic disease and RBC for wound infection based on logistic proportional regression analysis.

Parameters	Wound infection		
	OR	95% CI	P
Without basic disease*High RBC	1		
With basic disease*Low RBC	10.000	1.193–83.837	.034
With basic disease*High RBC	0.000	0.000–0.000	.999
Without basic disease*Low RBC	3.714	0.389–35.430	.254

OR = odds ratio, 95% CI = 95% confidence interval, RBC = red blood cell.
*$P < .05$.

3.6. ROC curve analysis

Finally, we constructed ROC curves to determine the effect of basic diseases, RBC, and their interaction on the occurrence of wound infection after osteosarcoma resection. And the AUC was used as the degree of confidence in judging each factor: basic diseases (AUC = 0.653, $P = .060$, 95% CI = 0.523–0.783), RBC (AUC = 0.653, $P = .060$, 95% CI = 0.523–0.783), and their interaction (AUC = 0.700, $P = .014$, 95% CI = 0.564–0.836) (Fig. 2).

4. Discussion

The study results showed a significant interaction between primary disease and RBC on postoperative orthopedic wound infection by binary logistic regression, identifying patients with the primary disease and low BRC as the population with postoperative orthopedic wound infection.

Additionally, prior research has demonstrated a connection between preoperative anemia and increased perioperative problems, such as postoperative wound infection and death.[12] An extensive study of the elderly in the United States described a 1.6% increase in postoperative mortality for every 1% change in hematocrit.[13] The current study also showed that low RBC is a risk factor for wound infection following osteosarcoma excision in terms of that procedure.[14] However, it is unclear whether anemia is mechanistically linked to the adverse outcomes we have described.[15] Existing studies suggest that the mechanism leading to the increased risk of wound infection after osteosarcoma resection includes reducing the oxygen-carrying capacity of the blood, thereby reducing the oxygen delivery to the end organs and tissues.[12] On this basis, our study further concluded that reduced oxygen delivery to end-organs will lead to many adverse consequences: first, the patient's tolerance to intraoperative or postoperative bleeding in osteosarcoma resection is reduced; second, the oxygen supply to the incision is significantly reduced, resulting in poor tissue healing and increasing the chance of wound infection. Following osteosarcoma resection, the reduced oxygen delivery to terminal organs caused by low RBC appears to be more pronounced and more likely to result in a wound infection because bone and surrounding tissues are typically supplied by periosteal arteries and nutrient arteries (all terminal arteries). In a retrospective cohort study of 2394 patients undergoing total knee arthroplasty, low RBC resulted in prolonged hospital stay,[16] and postoperative wound infection was one of the important reasons for prolonged hospital stay and increased medical costs.[17]

Our research also revealed that primary diseases before surgery contribute to wound infection following osteosarcoma excision. Consistent with the results of previous domestic studies, this may be because the combination of diabetes, hypertension, COPD, and other primary diseases can reduce the compensatory ability of essential organs. Surgical trauma will further reduce immunity, so the risk of wound infection is relatively increased.[18,19] For example, in patients with diabetes and other primary diseases, hyperglycemia can easily cause metabolic disorders, reduce the body's immunity, and quickly induce wound infection.[18] Therefore, elective surgery can be performed for patients with primary diseases before osteosarcoma resection to control the relevant indicators within the average range level to reduce the incidence of postoperative wound infection.

Our study summarized the causes as the combined effects of the following factors: primary diseases such as diabetes, hypertension, and atherosclerosis seriously affect the nutrient arteries and periosteal arteries of bone, resulting in their endothelial cell injury, vascular inflammation, etc.; ultimately leading to vascular lesions, local blood flow reduction and oxygen supply obstruction[20–22]; underlying pulmonary diseases such as chronic bronchopneumonia, which seriously affect the content of urea[23,24]; after osteosarcoma resection, the local blood vessels of the operation suffer a certain degree of damage; and low RBC reduces the red blood cell perfusion of the bone and surrounding soft tissues, resulting in the lack of oxygen supply to the osteosarcoma resection site. After a double blow from the primary disease with low RBCs, oxygen supply to the orthopedic surgical site is decreased, nutrition disorders, delayed wound healing, and increased risk of wound infection. Low RBC is associated with worse knee surgery outcomes and extended hospital stays (LOS).[25] Therefore, preoperative correction of low RBCs becomes an important medical cost control strategy. In addition, if the patient is to undergo elective osteosarcoma resection, the timing of surgery can be delayed until the risk factor is corrected. Blood management protocols of international

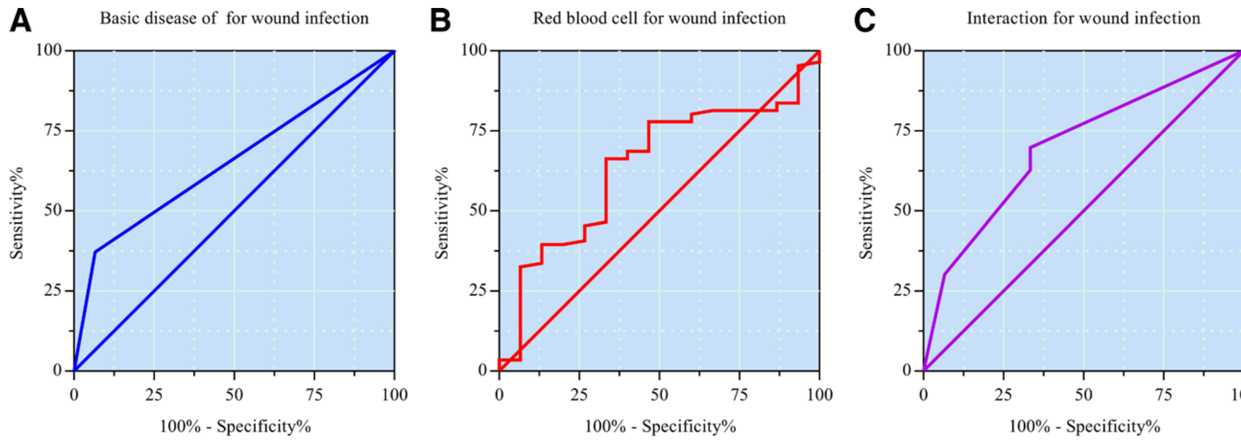

Figure 2. ROC curves to determine the effect of basic diseases, red blood cell, and their interaction on the occurrence of wound infection after osteosarcoma resection. ROC = receiver operating characteristic.

guidelines now also recommend early detection of preoperative anemia, identification of the cause, and treatment of any potentially reversible cause such as iron deficiency anemia.[26] Such prevention can reduce complications such as postoperative wound infection, postoperative blood transfusion, LOS, and readmission. In order to correct low RBC, manage the condition of primary diseases, and further assess the risk of postoperative wound infection in this patient undergoing elective osteosarcoma resection, active treatment should be given to this population before osteosarcoma resection after preoperative control of blood glucose, blood pressure, and other related indicators within the normal range.

Our study has some limitations. First, the cross-sectional design of this study makes it challenging to establish any causal relationship based on the collected data. To determine the factors that increase the incidence of postoperative wound infection in osteosarcoma excision, prospective and interventional studies are required. Second, the data collection method may have introduced a risk of bias.

5. Conclusion

In conclusion, patients with primary illnesses and low RBC risk developing an infection in the surgical site after removing osteosarcoma. Patients with these conditions make up most of those who get such an infection.

Author contributions

Conceptualization: Fei Chen.
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Formal analysis: Jie Wang, Xian-qiang Lv.
Software: Xin Zhao.
Supervision: Xin Zhao.
Writing – original draft: Fei Chen.
Writing – review & editing: Fei Chen.

References

[1] Devin CJ, Chotai S, McGirt MJ, et al. Intrawound vancomycin decreases the risk of surgical site infection after posterior spine surgery: a multicenter analysis. Spine (Phila Pa 1976). 2018;43:65–71.
[2] Backes M, Dingemans SA, Dijkgraaf M, et al. Effect of antibiotic prophylaxis on surgical site infections following removal of orthopedic implants used for treatment of foot, ankle, and lower leg fractures: a randomized clinical trial. JAMA. 2017;318:2438–45.
[3] Baranek ES, Tantigate D, Jang E, et al. Time to diagnosis and treatment of surgical site infections in foot and ankle surgery. Foot Ankle Int. 2018;39:1070–5.
[4] Owens PL, Barrett ML, Raetzman S, et al. Surgical site infections following ambulatory surgery procedures. JAMA. 2014;311:709–16.
[5] Tan T, Lee H, Huang MS, et al. Prophylactic postoperative measures to minimize surgical site infections in spine surgery: systematic review and evidence summary. Spine J. 2019;20:435–47.
[6] Uçkay I, Hoffmeyer P, Lew D, et al. Prevention of surgical site infections in orthopaedic surgery and bone trauma: state-of-the-art update. J Hosp Infect. 2013;84:5–12.
[7] Algra AM, Lindgren A, Vergouwen M, et al. Procedural clinical complications, case-fatality risks, and risk factors in endovascular and neurosurgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis. JAMA Neurol. 2019;76:282–93.
[8] Larcher A, Fossati N, Tian Z, et al. Prediction of complications following partial nephrectomy: implications for ablative techniques candidates. Eur Urol. 2016;69:676–82.
[9] Yuh BE, Nazmy M, Ruel NH, et al. Standardized analysis of frequency and severity of complications after robot-assisted radical cystectomy. Eur Urol. 2012;62:806–13.
[10] Elahi S. Neglected cells: Immunomodulatory roles of CD71+ erythroid cells. Trends Immunol. 2019;40:181–5.
[11] Kapadia BH, Berg RA, Daley JA, et al. Periprosthetic joint infection. Lancet. 2016;387:386–94.
[12] Fowler AJ, Ahmad T, Abbott T, et al. Association of preoperative anaemia with postoperative morbidity and mortality: an observational cohort study in low-, middle-, and high-income countries. Br J Anaesth. 2018;121:1227–35.
[13] Wu WC, Schifftner TL, Henderson WG, et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA. 2007;297:2481–8.
[14] Sebastian A, Huddleston P, 3rd, Kakar S, et al. Risk factors for surgical site infection after posterior cervical spine surgery: an analysis of 5,441 patients from the ACS NSQIP 2005-2012. Spine J. 2016;16:504–9.
[15] Baron DM, Hochrieser H, Posch M, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth. 2014;113:416–23.
[16] Abdullah HR, Sim YE, Hao Y, et al. Association between preoperative anaemia with length of hospital stay among patients undergoing primary total knee arthroplasty in Singapore: a single-centre retrospective study. BMJ Open. 2017;7:e016403.
[17] Allegranzi B, Bischoff P, de Jonge S, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16:e276–87.
[18] Amri R, Dinaux AM, Kunitake H, et al. Risk stratification for surgical site infections in colon cancer. JAMA Surg. 2017;152:686–90.
[19] Jackson SS, Leekha S, Magder LS, et al. Electronically available comorbidities should be used in surgical site infection risk adjustment. Clin Infect Dis. 2017;65:803–10.
[20] Hara T, Phuong PT, Fukuda D, et al. Protease-activated receptor-2 plays a critical role in vascular inflammation and atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2018;138:1706–19.
[21] Shah A, Gray K, Figg N, et al. Defective base excision repair of oxidative DNA damage in vascular smooth muscle cells promotes atherosclerosis. Circulation. 2018;138:1446–62.

[22] Shanbhogue VV, Hansen S, Frost M, et al. Bone disease in diabetes: another manifestation of microvascular disease. Lancet Diabetes Endocrinol. 2017;5:827–38.
[23] Albert RK, Au DH, Blackford AL, et al; Long-Term Oxygen Treatment Trial Research Group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N Engl J Med. 2016;375:1617–27.
[24] Waatevik M, Johannessen A, Gomez Real F, et al. Oxygen desaturation in 6-min walk test is a risk factor for adverse outcomes in COPD. Eur Respir J. 2016;48:82–91.
[25] Pitter FT, Jørgensen CC, Lindberg-Larsen M, Kehlet H; Lundbeck Foundation Center for Fast-track Hip and Knee Replacement Collaborative Group. Postoperative morbidity and discharge destinations after fast-track hip and knee arthroplasty in patients older than 85 years. Anesth Analg. 2016;122:1807–15.
[26] Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth. 2011;106:13–22.