Infection Control & Hospital Epidemiology (2022), **43**, 597–602
doi:10.1017/ice.2021.178

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Original Article

Association between blood transfusion and ventilator-associated events: a nested case-control study

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Abstract

Objectives: The association between blood transfusion and ventilator-associated events (VAEs) has not been fully understood. We sought to determine whether blood transfusion increases the risk of a VAE.

Design: Nested case-control study.

Setting: This study was based on a registry of healthcare-associated infections in intensive care units at West China Hospital system.

Patients: 1,657 VAE cases and 3,293 matched controls were identified.

Methods: For each case, 2 controls were randomly selected using incidence density sampling. We defined blood transfusion as a time-dependent variable, and we used weighted Cox models to calculate hazard ratios (HRs) for all 3 tiers of VAEs.

Results: Blood transfusion was associated with increased risk of ventilator-associated complication-plus (VAC-plus; HR, 1.47; 95% CI, 1.22–1.77; P <.001), VAC-only (HR, 1.29; 95% CI, 1.01–1.65; P = .038), infection-related VAC-plus (IVAC-plus; HR, 1.78; 95% CI, 1.33–2.39; P < .001), and possible ventilator-associated pneumonia (PVAP; HR, 2.10; 95% CI, 1.10–3.99; P = .024). Red blood cell (RBC) transfusion was also associated with increased risk of VAC-plus (HR, 1.34; 95% CI, 1.08–1.65; P = .007), IVAC-plus (HR, 1.70; 95% CI, 1.22–2.36; P = .002), and PVAP (HR, 2.49; 95% CI, 1.17–5.28; P = .018). Compared to patients without transfusion, the risk of VAE was significantly higher in patients with RBC transfusions of >3 units (HR, 1.73; 95% CI, 1.25–2.40; P = .001) but not in those with RBC transfusions of 0–3 units.

Conclusion: Blood transfusions were associated with increased risk of all tiers of VAE. The risk was significantly higher among patients who were transfused with >3 units of RBCs.

(Received 26 January 2021; accepted 28 March 2021; electronically published 17 May 2021)

In 2013, the US Centers for Disease Control and Prevention (CDC) released ventilator-associated event (VAE) definitions. To replace traditional concepts for surveillance of ventilator-associated pneumonia (VAP), the new definition was designed to identify a broad range of complications in patients receiving mechanical ventilation.[1,2] In 2019 in the United States, 2,028 hospitals were conducting VAE surveillance.[3,4] Recently, the new definition has been also adopted outside the United States.[5-7] Studies have suggested that VAE is common among patients receiving mechanical ventilation[5] and that a VAE may result in an adverse outcome, including death.[5,8,9]

However, sound evidence to support the management of VAE is lacking.[4,10] In 2015, Klompas[11] has proposed several potential strategies to prevent and control VAE. Some proposed interventions have effective[10,11]; however, the impact of other interventions, such as blood transfusion, is not yet fully understood.[11] Previous studies have reached conflicting conclusions.[12-16] Furthermore, only a limited number of studies have focused on VAE,[15,17] which typically involved small sample sizes and reached inconsistent conclusions. For instance, a nested case-control study including 192 pairs of children with ventilator-associated complication (VAC) and controls has demonstrated that blood product use was associated with a higher risk of VAC among patients admitted to the neonatal intensive care unit (ICU).[17] However, another case-control study has exhibited no difference between VAC and controls regardless of type or volume of blood transfusion.[15]

In 2015, West China Hospital (WCH) developed a prospective surveillance system for healthcare-associated infections (HAIs) in ICUs. As of December 31, 2018, nearly 30,000 ICU admissions had been monitored, and 1,800 were judged as VAE cases. Based on the surveillance system at WCH, we conducted a nested case-control

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Cite this article: Wang W, *et al.* (2022). Association between blood transfusion and ventilator-associated events: a nested case-control study. *Infection Control & Hospital Epidemiology*, 43: 597–602, https://doi.org/10.1017/ice.2021.178

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study with a relatively large sample size to evaluate the association between blood transfusion and risk of VAE.

Methods

This study followed the reporting standards according to Reporting of Studies Conducted Using Observational Routinely Collected Health Data[18] This study was reviewed and was approved by the West China Hospital Institutional Review Board (WCH2018-409).

Data source

We conducted a nested case-control study using ICU-HAI registry in the WCH system, which includes 3 independent healthcare institutions and is a national critical care center. The system provides tertiary care for Sichuan and other provinces.[19]

The ICU-HAI registry was developed by a integrating multi-source database, including the ICU-HAI system, ICU system, and electronic medical record (EMR) system.[20] The ICU-HAI system is a prospective surveillance system that monitors all patients admitted to ICUs. Information regarding catheterization, HAI, and prevention and control measures is actively collected by experienced infection control experts. This unique system for routine VAE surveillance in China monitors >5,000 cases of VAE every year. The ICU system contains information regarding vital signs, notes, life support, and risk assessments, which is electronically recorded by well-trained nurses. The EMR system contains patient-level clinical care information including demographics, laboratory test results, prescriptions, and diagnoses.[21] By integrating the 3 databases using a unique identifier, the ICU-HAI registry is a valuable data source for management of HAIs in the ICU setting.[20,22]

The ICU-HAI registry includes patients admitted to 6 ICUs in the WCH system starting April 1, 2015. As of December 31, 2018, the registry included 28,848 patients and 29,480 admissions. Previous studies showed that the registry had a high level of quality and comprehensiveness.[20,21,23,24]

Study cohort and design

Patients who consistently received mechanical ventilation for at least 4 days between April 1, 2015, and December 31, 2018, were identified from the registry. We excluded patients with incomplete information, those aged <18 years, those with extremely long hospital stays (>365 days), and those who did not pay for hospitalization because of a medical dispute. The clinical characteristics differed among non-VAE patients with and without consecutive stable or improved respiratory status. Therefore, we also excluded patients with consecutively unstable or increased minimum daily fraction of inspired oxygen (FiO_2) or positive end-expiratory pressure (PEEP) during the mechanical ventilation period. We additionally excluded 363 non-Chinese patients because many of them were transferred elsewhere and, therefore, the information regarding their clinical outcomes was incomplete.

We chose a case-control design nested within the cohort, to ensure identical duration of mechanical ventilation between patients with VAE and those without and to improve the efficiency of estimation of treatment effects.[25]

Case identification and control selection

We defined cases as patients with VAEs. VAE cases were judged according to the CDC criteria, defined as ≥2 days of increased FiO_2 or PEEP after ≥2 days of stable or improving ventilator settings.[1,2] All patients with a VAE were prospectively and actively identified from the ICU-HAI system. ICU nurses electronically recorded the value of FiO_2 and PEEP on an hourly basis. A threshold-based warning system was implemented in the ICU-HAI system. Once the value of FiO_2 or PEEP reached the threshold, an alarm was triggered. Thereafter, a team of infection control practitioners judged whether the patient had a VAE, and if so, classified VAE as VAC, infection-related ventilator-associated complication (IVAC), or possible ventilator-associated pneumonia (PVAP). Validation of PVAP showed that the consistency of this classification between 2 infection control practitioners was 96.2%. In this study, VAE cases were furtherly classified as (1) VAC-plus, defined as all patients with VAC, including those also met criteria for IVAC and PVAP; (2) VAC-only, defined as patients who met criteria for VAC, but not for IVAC and PVAP; (3) IVAC-plus, defined as patients with IVAC, including those also met criteria for PVAP; (4) PVAP.

For each VAE case, we randomly selected up to 2 controls from those still at risk for VAE at time of the case occurrence. We used incidence density sampling approach to match cases and controls with the same number of mechanical ventilation days (the number of days from the initiation of mechanical ventilation to VAE). We also matched cases and controls for age (<45, 45–59, 60–75, 75–89, and ≥90 years) and the number of days between ICU admission and initiation of mechanical ventilation. For VAE cases, only the first episode of VAE was measured if patient developed >1 episode of VAE; for non-VAE patients, only the first episode of mechanical ventilation was measured if patients had multiple mechanical ventilation treatments.

Blood transfusion and covariates

Blood transfusion was defined as administration of red blood cells (RBCs), platelet, or plasma. Information regarding blood transfusion was extracted from the physician's order of hospital information system. We measured blood transfusion as a time-varying variable. Daily blood transfusion from initiation of mechanical ventilation to the event of interest were calculated. We also measured daily RBC transfusion and transfusion volume from initiation of mechanical ventilation to the event of interest.

We identified potentially confounders from the ICU-HAI registry, including demographic characteristics, ICU type at admission, acute conditions, chronic comorbidities, APACHE II score at admission, daily fluid balance, medications, operations, and other treatments. Acute conditions, fluid balance, medications, and other treatments were measured from initiation of mechanical ventilation to the event of interest. Detailed description of covariates was listed in Table 2.

Information regarding medication was identified from prescription data, while chronic comorbidity information was identified from discharge diagnosis codes using the *International Classification of Diseases, Tenth edition*. With respect to acute comorbidities at ICU admission, we performed text mining by structuring the text information from the transfer records.

Statistical analysis

We assessed associations between blood transfusion (ie, RBC transfusion, plasma transfusion, platelet transfusion, and all blood transfusion types combined) and risk of VAE using weighted Cox proportional hazards model. The weighted Cox proportional hazard is a method that can estimate the effects of complex time-varying exposures in case–control studies.[26] Hazard ratios (HRs) for VAC-plus, VAC-only, IVAC-plus, and PVAP were

https://doi.org/10.1017/ice.2021.178 Published online by Cambridge University Press

Table 1. Characteristics of Cases and Matched Controls

Characteristics	Overall (n=4,950)	Cases (n=1,657)	Controls (n=3,293)	*P* Value
Age, median y [IQR]	59 [46–69]	58 [46–69]	59 [46–70]	.475
Sex, male, no. (%)	3,122 (63.1)	1,056 (63.7)	2,066 (62.7)	.516
Intensive care unit type, no. (%)				<.001
General ICU	1,684 (34.0)	562 (33.9)	1,122 (34.1)	
Neurological ICU	931 (18.8)	344 (20.8)	587 (17.8)	
Respiratory ICU	823 (16.6)	169 (10.2)	654 (19.9)	
Surgical ICU	991 (20.0)	459 (27.7)	532 (16.2)	
Thoracic ICU	521 (10.5)	123 (7.4)	398 (12.1)	
Acute conditions at admission, no. (%)				
ARDS	61 (1.2)	17 (1.0)	44 (1.3)	.425
Shock	283 (5.7)	96 (5.8)	187 (5.7)	.921
Gastrointestinal bleeding	76 (1.5)	24 (1.4)	52 (1.6)	.818
Pneumonia	475 (9.6)	161 (9.7)	314 (9.5)	.878
Chronic comorbidities, no. (%)				
Diabetes	260 (5.3)	73 (4.4)	187 (5.7)	.068
Cardiovascular disease	31 (0.6)	11 (0.7)	20 (0.6)	.963
Heart failure	473 (9.6)	131 (7.9)	342 (10.4)	.006
Chronic lung disease	272 (5.5)	79 (4.8)	193 (5.9)	.127
Malignant tumor	422 (8.5)	130 (7.8)	292 (8.9)	.246
Liver failure	106 (2.1)	42 (2.5)	64 (1.9)	.211
Hypertension	1043 (21.1)	346 (20.9)	697 (21.2)	.845
Kidney failure	396 (8.0)	150 (9.1)	246 (7.5)	.06
APACHE II, median score [IQR]	20 [15–25]	20 [15–25]	20 [15–25]	.727
Tracheotomy	471 (9.5)	195 (11.8)	276 (8.4)	<.001
Hemoglobin at ICU admission, g/L [IQR]	101 [84–120]	101 [84–121]	102 [84–120]	.940
Outcomes				
Hospitalization, median d [IQR]	24 [16–37]	27 [17–41]	24 [16–36]	<.001
ICU stay, median d [IQR]	16 [10–25]	18 [11–30]	14 [9–23]	<.001
MV, median d [IQR]	10 [6–18]	13 [8–21]	9 [6–15]	<.001
Hospital mortality, no. (%)	813 (16.4)	337 (20.3)	476 (14.4)	<.001

Note. IQR, interquartile range; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; MV, mechanical ventilation.

calculated. We also measured the associations between RBC transfusion volume and the risk of all tiers of VAEs. Hazard ratios of RBC transfusions of 0–3 units and RBC transfusions of >3 units were also calculated.

All analyses were adjusted using a combination of fixed and time-varying covariates (Table 2). Time-varying variables including daily exposure to medication and process were measured with respect to whether each treatment was performed on each day from the initiation of mechanical ventilation to events of interest. We used multiple imputation to handle missing data of APACHE II score and fluid balance. The proportions of missing data for APACHE II score and fluid balance were 10.2% and 7.0%, respectively. Compared with single imputation (eg, mean or regression imputations), multiple imputation considers uncertainty behind missing value estimations, which is considered superior to single imputation.[27]

Sensitivity analyses

We conducted several sensitivity analyses to evaluate the robustness of effect estimates: (1) alternative definition of blood transfusion: daily blood transfusion within 4 days prior to the event of interest; (2) alternative approach for missing data: complete case analysis without imputation; and (3) alternative inclusion and exclusion criteria: excluding patients who developed VAE within 4 days after mechanical ventilation began.

Results

In total, 29,480 patients were assessed for eligibility. After exclusion, 6,176 patients receiving mechanical ventilation consistently for at least 4 days and with at least consecutive 2 days of stable or improved respiratory function were included in the initial cohort. After performing incidence density sampling, 1,657

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Table 2. Associations Between Blood Transfusion and Risk of VAE[a]

	VAC Plus		VAC Only		IVAC Plus		PVAP	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Blood transfusion	1.47 (1.22–1.77)	<.001	1.29 (1.01–1.65)	.038	1.78 (1.33–2.39)	<.001	2.10 (1.10–3.99)	.024
RBC transfusion	1.34 (1.09–1.65)	.006	1.14 (0.86–1.50)	.36	1.70 (1.22–2.36)	.002	2.49 (1.17–5.28)	.018
Without RBC transfusion	Reference		Reference		Reference		Reference	
Transfused red cell 0–3 units	1.18 (0.92–1.50)	.193	1.01 (0.73–1.38)	.977	1.52 (1.03–2.24)	.037	2.05 (0.82–5.17)	.126
Transfused red cell >3 units	1.73 (1.25–2.40)	.001	1.50 (0.96–2.35)	.074	2.11 (1.24–3.58)	.006	3.37 (1.08–10.47)	.036
Plasma transfusion	1.39 (1.10–1.75)	.006	1.21 (0.90–1.63)	.211	1.82 (1.22–2.70)	.003	1.82 (0.76–4.37)	.181
Platelet transfusion	1.13 (0.76–1.69)	.538	0.98 (0.57–1.68)	.936	1.33 (0.72–2.44)	.359	1.57 (0.45–5.56)	.481

Note. VAE, ventilator-associated events; IVAC, infection-related ventilator associated complication, PVAP, possible ventilator-associated pneumonia; RBC, red blood cell.
[a]Model adjusted for ICU type, acute conditions (ie, acute respiratory distress syndrome, shock, gastrointestinal bleeding, and pneumonia), chronicity comorbidities (ie, malignant tumor, chronic lung disease, cardiovascular disease, congestive heart failure, liver and renal failure, and diabetes), APACHE II score at admission, daily fluid balance, medications (ie, neuroleptic agents, opioids, sedative, thromboembolism prophylaxis, acid inhibitors, neuromuscular blockers, intestinal probiotics, expectorant, antibiotics, immunosuppressive agent, and vasopressors), operation and other treatment (ie, cranial or cardiac surgery, fiberoptic bronchoscopy examination, gastrointestinal decompression, tracheotomy, mandatory ventilation, enteral nutrition, esophagogastroduodenoscopy, and head-of-bed elevation).

patients with VAE and 3,293 matched controls were finally included. Among patients with VAE, the median day from initiation of mechanical ventilation to VAE was 4 days (interquartile range [IQR], 3–8), and the median day from first blood transfusion to VAE was 3 days (IQR, 2–6).

The median age was 59 years (IQR, 46–69), and 3,122 patients (63.1%) were male. The distribution of ICUs differed among cases and controls. In total, 27.7% patients with VAE and 16.2% of controls were admitted to the surgical ICU. The most common acute conditions were pneumonia (9.6%) and shock (5.7%), and the most common comorbidities were hypertension (21.1%), heart failure (9.6%), and malignant tumor (8.5%). The proportions of comorbidities and acute conditions were similar in cases and controls, except for heart failure. The proportion of heart failure was higher in controls than in patients with VAEs (10.4% vs 7.9%; $P = .006$). The median hemoglobin at ICU admission was 101 g/L (IQR, 84–120), which was similar in cases and controls (101 g/L; [IQR, 84–121] and 102 g/L [IQR, 84–120], respectively; $P = .94$) (Table 1).

Compared with controls, the median hospitalization stays (27 days [IQR, 17–41] vs 24 days [IQR, 16–36] days; $P < .001$), ICU stays (18 days [IQR, 11–30] vs 14 days [IQR, 9–23]; $P < .001$), and mechanical ventilation days (13 days [IQR, 8–21] vs 9 days [IQR, 6–15]; $P < .001$) were longer among patients with VAE. The crude mortality rate among patients with VAEs were also higher than those without a VAE (20.3% vs 14.4%; $P < .001$) (Table 1).

Blood transfusion among included patients

Among 1,675 patients with VAEs, 802 (48.4%) received blood transfusions. Of these, 652 (39.3%) received RBC transfusions, 487 (29.4%) received plasma transfusions, and 168 (10.1%) received platelet transfusions. The median number of units of transfused RBC was 0 (IQR, 0–3.5) among patients with VAEs (Supplementary Table 1 online). The proportion of patients receiving blood transfusion among controls were similar to those in the VAE group. Among those who did not experience a VAE, 1,216 (36.9%) patients received RBC transfusions, 921 (28.0%) received plasma transfusions, and 404 (12.3%) received platelet transfusions (Supplementary Table 1 online).

Associations between blood transfusion and VAE

We summarized associations between blood transfusion and risk of VAE (Table 2). Compared to no blood transfusion, blood transfusions from initiation of mechanical ventilation to the events of interest were associated with significantly higher hazards for VAC-plus (HR, 1.47; 95% CI, 1.22–1.77; $P < .001$), VAC-only (HR, 1.29; 95% CI, 1.01–1.65; $P = .038$), IVAC-plus (HR, 1.78; 95% CI, 1.33–2.39; $P < .001$), and PVAP (HR, 2.10; 95% CI, 1.10–3.99; $P = .024$). RBC transfusions were associated with increased risk of VAC-plus (HR, 1.34; 95% CI, 1.09–1.65; $P = .006$), IVAC-plus (HR, 1.70; 95% CI, 1.22–2.36; $P = .002$), and PVAP (HR, 2.49; 95% CI, 1.17–5.28; $P = .018$), but not with significantly increased risk of VAC-only (HR, 1.14; 95% CI, 0.86–1.50; $P = .36$). Plasma transfusions were associated with significantly higher risk of VAC-plus (HR, 1.39; 95% CI, 1.10–1.75; $P = .006$) and IVAC-plus (HR, 1.82; 95% CI, 1.22–2.70; $P = .003$); however, no statistically significant increase in VAC-only (HR, 1.21; 95% CI, 0.90–1.63; $P = .211$) or PVAP (HR, 1.82; 95% CI, 0.76–4.37; $P = .181$) was detected. We detected no statistically significant increase in all tiers of VAE for platelet transfusions (Table 2).

Compared to patients without RBC transfusions, patients with RBC transfusions of >3 units had significantly higher hazards for VAC-plus (HR, 1.73; 95% CI, 1.25–2.40; $P = .001$) than those without RBC transfusions. However, RBC transfusion of 0–3 units was not associated with significantly higher hazard for VAC-plus compared to treatment without RBC transfusion (HR, 1.18; 95% CI, 0.92–1.50; $P = .193$). Compared to those without blood transfusion, the risk of IVAC-plus was significantly higher both in patients with RBC transfusions of >3 units (HR, 2.11; 95% CI, 1.24–3.58; $P = .006$) and those with RBC transfusions of 0–3 units (HR, 1.52; 95% CI, 1.03–2.24; $P = .037$). The risk of PVAP was significantly higher in patients with RBC transfusions of >3 units (HR, 3.37; 95% CI, 1.08–10.47; $P = .036$) but not in those with RBC transfusions of 0–3 units (HR, 2.05; 95% CI, 0.82–5.17; $P = .126$) (Table 2).

Sensitivity analyses

Sensitivity analyses using alternative definition of exposure showed similar results. The results were consistent among the subset of

https://doi.org/10.1017/ice.2021.178 Published online by Cambridge University Press

patients with complete data (N = 3,501) for all transfusion types combined, but the confidence interval crossed 1 for RBCs alone (HR, 1.30; 95% CI, 0.97–1.74; $P = .083$). The sensitivity analysis excluding patients who developed VAE within 4 days of mechanical ventilation initiation (N = 2,439), the hazard ratios for all blood transfusion types combined was similar to the primary analysis but with wider confidence intervals that crossed one (HR, 1.25; 95% CI, 0.93–1.67; $P = .138$) (Supplementary Table 2 online).

Discussion

The main finding of this study was that blood transfusion, especially RBC transfusion, was common among patients in the ICU who received mechanical ventilation. Compared to those who did not receive blood transfusions, patients who received blood transfusions had significantly higher risks for all tiers of VAEs. The risks were significantly higher among patients who received RBC transfusions of >3 units than among those who did not.

Conservative blood transfusion has been proposed as a potential strategy to prevent VAEs.[11] The findings of this study lend further support to this strategy. The reason for the increased risk of VAE may have been increased risk of infection, and in part, volume overload. Our study showed that blood transfusion increased the risk of both infection-related and non–infection-related complications, which supports the hypothesis. Blood transfusions have been shown to have important effects on immunologic function, increasing the risk of infection.[28,29] In vitro studies have shown that allogeneic transfusion may induce dysregulation of inflammation, downregulation of cellular host defenses, and enhanced B-cell function.[29,30] Indeed, several clinical studies have demonstrated a higher risk of infections among transfused patients versus those without.[29,31,32] A study involving 1,717 ICU patients found that RBC transfusion was associated with a higher risk of nosocomial infections; the infection rates in the transfusion and the nontransfusion group were 15.38% and 2.92%, respectively.[31] Infection, especially pulmonary infection, may further lead to respiratory deterioration and VAEs. Moreover, volume overload may be another potential mechanism for VAEs. Patients receiving a blood transfusion have a higher risk of circulatory overload.[11,12] A randomized controlled trial suggested that, compared with a liberal strategy, a restrictive transfusion strategy was associated with decreased risk of cardiac complications, such as pulmonary edema.[12] A systematic review also showed that a restrictive transfusion strategy was associated with a significantly lower hazard for pulmonary edema compared to a liberal strategy.[13]

Some studies, however, have not shown significant associations between blood transfusions and risk of VAE.[15,17] The potential reason for the inconsistent conclusion may be partly due to the heterogeneity of included patients. The effects of blood transfusion on adverse outcomes varied among patients with various comorbidities.[15,16] Moreover, the number of RBC units transfused may also be associated with adverse outcomes. A study showed that the risk of infection increased 9.7% for every unit increase in RBCs transfused.[32] Our study also showed that patients transfused with >3 RBC units has an increased risk of all 3 tiers of VAEs; however, no significant differences were detected for the risk of VAE and PVAP among patients who received transfusion of <3 RBC units.

This study has several strengths. The sample size was relatively large, and it included thousands of patients with VAE. We identified VAE cases from a prospective system that routinely underwent VAE surveillance for all patients admitted to ICUs. The accuracy of PVAP has been shown to be high. We considered blood transfusions as time-varying variates and adjusted for an extensive array of potential confounders.

However, our study has several limitations. First, this was an observational study. Although we performed a number of statistical models, residual confounding factors remained. Second, due to the observational nature of the study, blood transfusion was not randomly performed but was left to the discretion of physicians. Information regarding the indication of blood transfusion was lacking, which may have led to indication bias. Third, transfusion strategies vary among individual clinicians, and we were unable to determine the optimal transfusion trigger, and assess the association between the rate of transfusion and VAE. Finally, we collected data from a homogeneous healthcare system; therefore, our findings may not be generalizable.

Acknowledgments.

Financial support. W.W. received grant support from the National Key Research and Development Program of China (grant no. 2020YFC2009003). X.S. received grant support from Sichuan Youth Science and Technology Innovation Research Team (grant no. 2020JDTD0015) and the 1·3·5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (grant no. ZYYC08003). Z.Y.Z. received grant support the 1·3·5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (grant no. ZYYC08006).

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2021.178

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https://doi.org/10.1017/ice.2021.178 Published online by Cambridge University Press