Research Article

Week-One Anaemia was Associated with Increased One-Year Mortality in Critically Ill Surgical Patients

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Received 28 May 2022; Revised 15 August 2022; Accepted 16 August 2022; Published 6 September 2022

1.Introduction

Anaemia is a highly prevalent comorbidity in critically ill surgical patients, and it is estimated that approximately 50% of critically ill patients experience anaemia. [1–4] A number of evidence have shown that anaemia has a deleterious impact on the outcome in patients undergoing surgery. [5–7] Baron et al. conducted a multicentre study with 39,309 patients undergoing in-patient surgery in 28 European nations and implicated anaemia with poor postsurgery outcomes, including hospital length of stay, postoperative admission to intensive care, and in-hospital mortality [5]. Similarly, Musallam et al. analysed data of 211 hospitals worldwide with 227,425 patients and found that mild anaemia, defined by haematocrit concentration <39%, (1.41, 95% CI 1.30–1.53) and moderate-to-severe anaemia, defined by haematocrit concentration <30%, (1.44, 95% CI 1.29–1.60) were associated with an increased risk of 30-day morbidity in patients undergoing major noncardiac surgery [6].

In addition to the aforementioned evidence among in-patient surgical patients, Hammer et al. focused on critically
ill surgical patients and investigated factors associated with being readmitted to the intensive care units (ICUs) among 7,126 critically ill surgical patients at Beth Israel Deaconess Medical Center between 2015 and 2019. [7] Hammer et al. reported that severe anaemia (haemoglobin <7 mg/dl) was a crucial risk factor of being readmitted to ICU during the same hospitalisation. [7] Our recently published study, using an explainable machine learning approach to establish a long-term mortality prediction model in critically ill patients, found that levels of haemoglobin lower than 10 g/dL was a crucial feature with high feature importance in the long-term mortality prediction model [8]. Therefore, there is an essential need to address the long-term mortality impact of anaemia in critically surgical ill patients. In the present study, we linked the critical care database at a tertiary referral centre in central Taiwan with the population-based death-registry file in Taiwan to address the prevalence of anaemia and to investigate the long-term mortality association of anaemia in critically ill surgical patients.

2. Materials and Methods

2.1. Ethical Approval. The retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Taichung Veterans General Hospital (TCVGH: SE210988B). The informed consent was waived due to all of the data analysed were deidentified data.

2.2. Study Population. This retrospective cohort study enrolled consecutive patients who were admitted to surgical ICUs at TCVGH, a tertiary referral centre with 48 surgical ICU beds in central Taiwan, between 2015 and 2020. The first ICU admission was used among patients with more than one ICU admission. We used the average level of haemoglobin among those with more than one measurement of haemoglobin, and patients without data regarding the level of haemoglobin within the first week were excluded from analyses.

2.3. Primary Outcome. The main outcome of interest was the one-year all-cause mortality, and we retrieved the date-of-death from the nationwide death registration profile of the National Health Insurance Research Database (NHIRD) in Taiwan [9]. Taiwan has implemented a compulsory National Health Insurance (NHI) program since 1995, with nearly 99.9% coverage of the Taiwanese population in 2019; therefore, the date-of-death among enrolled participants in the present study can be ascertained.

2.4. Covariates. The TCVGH critical care data warehouse was used to retrieve data with respects to demographic data, Charlson comorbidity index (CCI), Acute Physiology and Chronic Health Evaluation (APACHE) II score, presence of shock, receiving mechanical ventilation, underwent renal replacement, management including blood transfusion, and laboratory data [10]. Previous studies, including our studies, have shown the mortality association of early (day 1–3) overall fluid balance status and culture positivity of microbial culture during ICU admission, we hence included these two variables as covariates in the present study [11–13].

2.5. Statistical Analyses. Data were represented as means ± standard deviation or number (percentages). We used a Cox proportional hazards model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for one-year all-cause mortality after adjustment for potential cofounders. Variables were included in the multivariable model if the associated univariable P value was <0.20 and the variance inflation factor was <10. [14] Statistical analyses were two-sided, and the level of significance was set at 0.05. Data analysis was conducted using R version 3.6.0.

2.6. Sensitivity Analyses. In the present study, we further utilised propensity score matching (PSM) and two weighting methods, including the inverse probability of treatment weight (IPTW) and covariate balancing propensity score (CBPS), to determine the impact of week-one anaemia on the one-year all-cause mortality. [15, 16] In PSM, we used the optimal nearest neighbour matching algorithm, and the calliper distance of standard mean difference was 0.10. The PSM is designed to construct a control group with matched anaemia-associated covariates, but a number of cases were inevitably excluded due to the lack of matched controls. Therefore, the restricted subpopulation might not fully represent the original population. [15] The IPTW, a propensity score weighting method, has been proposed to include the whole population for analyses, but the extreme weight at the tails among the distribution of propensity scores might compromise the balance among covariates [17, 18]. The CBPS, a novel propensity score weighting method, is increasingly used given that CBPS includes the whole study population through weighting and optimises the balance among covariates [16, 19].

3. Results

3.1. Characteristics of the Enrolled Patients and the Propensity Score-matched Population. Figure 1 shows the process of patient enrollment of the primary cohort (n=7,623) and propensity core-matched cohort (n=3,002) divided by the average level of week-one levels of haemoglobin lower and higher/equal than 10 g/dL (Figure 1). A total of 7,623 patients were included for analyses, and patients with anaemia had a higher proportion of one-year mortality compared with those without anaemia (42.0% vs 17.3%) (Table 1). We found that patients with anaemia had a higher age (64.4 ± 16.3 vs 59.6 ± 15.7 years), slightly lower body mass index (23.8 ± 4.6 vs 24.4 ± 4.5), more comorbidities (CCI 2.0 ± 1.6 vs 1.4 ± 1.3), and more blood loss in the operating room (404.8 ± 612.6 vs 326.2 ± 527.9 mL) compared those without anaemia. The disease severity was higher in those with anaemia, including a higher APACHE II score (22.7 ± 6.6 vs 19.6 ± 5.5) as well as more likely to have shock (50.3% vs 25.3%), to receive emergent surgery (8.0% vs
3.2. Association between Anaemia in the First Week and One-Year Mortality. We employed the multivariable Cox proportional hazards model to identify independent one-year mortality predictors in 7,623 critically ill surgical patients. We identified that week-one anaemia (aHR, 1.17; 95% CI, 1.045–1.310) correlated with an increased risk of one-year mortality after adjusting for relevant covariates (Table 2). We then used the propensity score-based approach to further clarify the aforementioned association between week-one anaemia and one-year mortality in critically ill surgical patients. Figure 2 demonstrates the overall quality of the matching, which was evaluated by comparing the standardised difference of the means as well as the ratio of the variances (Figure 2). The quality of matching was high, with the standardised difference of covariates being lower than 0.10. We adjusted the covariates step-by-step, including demographic and comorbidities in model 2, critical illness relevant disease severity and managements in model 3, and laboratory data in model 4 (Table 3) (See detailed data in supplemental Table 1). We found a consistent strength of association between week-one anaemia and increased risk for one-year mortality in distinct cohorts, with the adjusted HRs in the PSM, IPTW, and CBPS were 1.164 (95% CI 1.025–1.322), 1.179 (95% CI 1.030–1.348), and 1.181 (1.034–1.349), respectively.

4. Discussion

In the present study, we used propensity score-matched and -weighted methods to determine the association between week-one anaemia and one-year mortality in critically ill surgical patients. We found that approximately one-third of critically ill surgical patients had anaemia within the first week, and week-one anaemia was associated with a 29.8% increase of the hazard ratio for one-year mortality. The positive association between week-1 anaemia and one-year mortality in critically ill surgical patients was robust in propensity score-based analyses, including PSM, IPTW, and CBPS. Our findings suggest that anaemia appears to be a predictor and modifiable factor for long-term mortality in critically ill surgical patients.
A number of studies have shown the short-term impact of anaemia in critically ill patients, and a few studies have explored the prolonged impact of anaemia after discharge. But, few studies have focused on critically ill surgical patients, particularly the long-term mortality impact of anaemia. Shah et al. recently conducted 1,174 ICU patients who were discharged from two mixed medical and surgical ICUs in the United Kingdom (UK) and found that patients discharged from ICU with anaemia (Hb < 10 g/dL) had a longer post-ICU hospital length of stay compared with those in critically patients without anaemia (8 vs 3 days, \( p = 0.0017 \)). [3] Indeed, the majority (65.5%, 769/1,174) of enrolled subjects in the aforementioned study were critically ill surgical patients. Similarly, van der Laan et al. analysing 6,358 ICU survivors, mainly discharged from surgical ICU (60.7%, 3860/6358), in Western Australia, found that 45.4% (2,886/6,358) of patients had anaemia (<10 g/dL), which correlated with decreased days at home till day-90 (Relative risk 0.96, 95% CI 0.93–0.98). [4] Notably, anaemia in critically ill patients appears to be a lasting issue. Warner et al. analysed levels of haemoglobin at 3-month, 6-month, and 12-month after ICU discharge among 6,901 critically ill patients in Minnesota and reported that the prevalence of anaemia at 3-month, 6-month, and 12-month were 56%, 52%, and 45%, respectively [21]. These evidence highlight the impacts of anaemia and indicate the need to explore the long-term impact of anaemia in critically ill surgical patients as we have shown in the present study.

The propensity score-based analysis is a statistical approach attempting to reduce selection bias and the confounding effect in an observational study [15]. The propensity score-matching analyses have been widely used, but the matched population may not fully represent the original population [23]. The IPTW overcame the aforementioned issue through weighting the overall enrolled subjects, but extreme propensity scores could bias the estimator and result in excessive variance [18]. Therefore, CBPS is proposed through estimating propensity scores that

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**Table 1: Characteristics between the patients categorised by week-1 level of haemoglobin in the primary cohort and propensity score-matched cohort.**

| Outcome | Before PSM | 1:1 PSM |
|---------|------------|---------|
| | Hb < 10 | Hb ≥ 10 | SMD | Hb < 10 | Hb ≥ 10 | SMD |
| **Basic characteristics** | | | | | | |
| Age, years | 64.4 ± 16.3 | 59.6 ± 15.7 | 0.304 | 63.3 ± 16.5 | 63.2 ± 15.6 | 0.007 |
| Sex (male) | 1422 (62.4%) | 3423 (64.1%) | 0.035 | 946 (63.0%) | 946 (63.0%) | <0.001 |
| Body mass index | 23.8 ± 4.6 | 24.4 ± 4.5 | 0.140 | 23.9 ± 4.6 | 23.8 ± 4.6 | 0.022 |
| Charlson comorbidity index | 2.0 ± 1.6 | 1.4 ± 1.3 | 0.410 | 1.8 ± 1.5 | 1.8 ± 1.5 | 0.025 |
| **Severity and managements** | | | | | | |
| APACHE II score | 22.7 ± 6.6 | 19.6 ± 5.9 | 0.505 | 21.6 ± 6.4 | 21.2 ± 6.0 | 0.057 |
| Presence of shock | 1147 (50.3%) | 1353 (25.3%) | 0.533 | 663 (44.2%) | 663 (44.2%) | <0.001 |
| Emergent surgery | 183 (8.0%) | 106 (2.0%) | 0.280 | 69 (4.6%) | 71 (4.7%) | 0.006 |
| **Surgical divisions** | | | | | | |
| Cardiovascular surgery | 456 (20.0%) | 811 (15.2%) | 0.127 | 386 (25.7%) | 386 (25.7%) | <0.001 |
| Neurosurgery | 263 (11.5%) | 2293 (42.9%) | 0.753 | 246 (16.4%) | 246 (16.4%) | <0.001 |
| Major abdomen surgery | 328 (14.4%) | 172 (3.2%) | 0.402 | 132 (8.8%) | 132 (8.8%) | <0.001 |
| Others | 495 (21.7%) | 558 (10.4%) | 0.310 | 281 (18.7%) | 281 (18.7%) | <0.001 |
| Blood loss at operating room, ml | 404.8 ± 221.2 | 326.2 ± 257.9 | 0.137 | 463.1 ± 633.1 | 464.5 ± 649.3 | 0.002 |
| Receiving RBC transfusion | 1890 (82.9%) | 1785 (33.4%) | 1.160 | 1110 (74.5%) | 1110 (74.5%) | 0.034 |
| Receiving mechanical ventilation | 1771 (77.7%) | 3500 (65.5%) | 0.272 | 1133 (75.5%) | 1174 (78.2%) | 0.065 |
| Receiving RRT | 362 (15.9%) | 108 (2.0%) | 0.500 | 122 (8.1%) | 99 (6.6%) | 0.059 |
| End-stage renal disease | 92 (4.0%) | 25 (0.5%) | 0.242 | 31 (2.1%) | 23 (1.5%) | 0.040 |
| Fluid balance day 1–3 | 1649.9 ± 3010.0 | 659.7 ± 2062.9 | 0.384 | 1435.1 ± 2805.6 | 1159.2 ± 2474.7 | 0.104 |
| Positive microbiological culture | 1161 (50.9%) | 1404 (26.3%) | 0.523 | 675 (45.0%) | 640 (42.6%) | 0.047 |
| Laboratory data | | | | | | |
| White blood cell count (10⁹ [3/µL] | 11049.6 ± 5620.9 | 10792.5 ± 3888.1 | 0.053 | 10903.7 ± 5198.4 | 11147.5 ± 4159.1 | 0.052 |
| Platelet (10³ [µL] | 167.6 ± 99.8 | 206.6 ± 80.7 | 0.430 | 173.7 ± 100.2 | 178.5 ± 87.4 | 0.052 |
| Albumin (mg/dL) | 3.0 ± 0.7 | 3.7 ± 0.7 | 0.936 | 3.2 ± 0.7 | 3.2 ± 0.7 | 0.040 |
| Creatinine (mg/dL) | 2.0 ± 2.1 | 1.0 ± 0.9 | 0.607 | 1.6 ± 1.8 | 1.3 ± 1.4 | 0.236 |

Data are shown as mean ± standard deviation and number (percentages). PSM, propensity score-matching; SMD, standard mean difference; Hb, haemoglobin (g/dL); APACHE, Acute Physiology and Chronic Health Evaluation; RBC, red blood cell; RRT, renal replacement therapy; ICU, intensive care unit.
covariate balance and prediction of treatment assignment are both maximized [16]. The subject number in the present study was high, and standardised mean differences between the two groups among variables were apparently low (Figure 2). Therefore, we identified a similar strength of association between week-one anaemia and one-year mortality among the three propensity score-based analyses.

Anaemia in critically ill surgical patients may result from a wide range of etiologies, consisting of blood loss, persistent/dysregulated inflammation, deficiency of erythropoietin, impaired erythropoietic response, and nutritional deficiencies [2, 24]. Unlike chronic anaemia, inflammation-associated impaired iron metabolism plays a crucial role in the pathogenesis of anaemia among critically ill patients, so-called anaemia of inflammation [25]. Alamo et al. using a rodent model with lung injury and hemorrhagic shock to mimic persistent injury-associated anaemia, demonstrated not only decreased erythropoietin receptor expression

### Table 2: Cox proportional hazards regression for one-year mortality among 7,623 critically ill surgical patients.

| Characteristics                      | Univariable | p value | Multivariable | p value |
|--------------------------------------|-------------|---------|---------------|---------|
| **Basic characteristics**            |             |         |               |         |
| Age, per 1 year increment            | 1.026 (1.023–1.029) | <0.001  | 1.007 (1.004–1.010) | <0.001  |
| Male gender                          | 1.246 (1.131–1.372) | <0.001  | 1.144 (1.037–1.262) | 0.007   |
| Body mass index, per 1 increment     | 0.946 (0.936–0.957) | <0.001  | 0.964 (0.953–0.974) | <0.001  |
| Charlson comorbidity index           | 1.308 (1.274–1.343) | <0.001  | 1.168 (1.134–1.202) | <0.001  |
| **Severity and managements**         |             |         |               |         |
| APACHE II score, per 1 increment     | 1.130 (1.121–1.139) | <0.001  | 1.058 (1.049–1.068) | <0.001  |
| Presence of shock                    | 2.533 (2.314–2.773) | <0.001  | 1.508 (1.361–1.671) | <0.001  |
| **Surgical divisions**               |             |         |               |         |
| Cardiovascular surgery               | 0.366 (0.309–0.435) | <0.001  | 0.266 (0.221–0.320) | <0.001  |
| Neurosurgery                         | 0.446 (0.398–0.499) | <0.001  | 0.612 (0.539–0.697) | <0.001  |
| Major abdomen surgery                | 1.986 (1.722–2.290) | <0.001  | 0.712 (0.612–0.827) | <0.001  |
| Receiving RBC transfusion            | 2.452 (2.227–2.700) | <0.001  | 1.012 (0.894–1.146) | 0.851   |
| Receiving mechanical ventilation     | 1.708 (1.531–1.905) | <0.001  | 1.093 (0.970–1.231) | 0.146   |
| Receiving renal replacement therapy  | 4.050 (3.574–4.590) | <0.001  | 1.422 (1.235–1.637) | <0.001  |
| Fluid overload, day 1–3, per 1 litre increment | 1.166 (1.149–1.183) | <0.001  | 1.036 (1.019–1.054) | <0.001  |
| Positive microbiological culture     | 3.054 (2.787–3.346) | <0.001  | 1.298 (1.165–1.446) | <0.001  |
| **Laboratory data**                  |             |         |               |         |
| Platelet (per 10^13/μL increment)    | 0.995 (0.994–0.995) | <0.001  | 0.998 (0.998–0.999) | <0.001  |
| Albumin (per 1 mg/dL increment)      | 0.434 (0.407–0.464) | <0.001  | 0.766 (0.709–0.827) | <0.001  |
| Haemoglobin <10 g/dL                 | 2.880 (2.631–3.153) | <0.001  | 1.710 (1.045–1.310) | 0.007   |

PSM, propensity score matching; IPTW, inverse probability of treatment weighting; CBPS, covariate balancing propensity score; HR, hazard ratio; CI, confidence interval.

**Figure 2**

**Table 3: Cox proportional hazard regressions for estimation of the association between level of week-1 haemoglobin lower than 10 g/dL and one-year mortality in critically ill patients.**

| Model | PSM HR (95%CI) | IPTW HR (95%CI) | CBPS HR (95%CI) |
|-------|----------------|-----------------|-----------------|
| 1     | 1.264 (1.115–1.434) | 1.208 (1.042–1.400) | 1.307 (1.140–1.498) |
| 2     | 1.249 (1.101–1.417) | 1.184 (1.029–1.362) | 1.246 (1.092–1.421) |
| 3     | 1.170 (1.030–1.329) | 1.175 (1.026–1.347) | 1.186 (1.037–1.356) |
| 4     | 1.164 (1.025–1.322) | 1.179 (1.030–1.348) | 1.181 (1.034–1.349) |

Model 1: Unadjusted. Model 2: Adjusted for demographic data and comorbidities listed in Table 1. Model 3: Adjusted for variables in model 2 and critical illness severity as well as managements listed in Table 1. Model 4: Adjusted for variables in model 3 and laboratory data listed in Table 1. PSM, propensity score matching; IPTW, inverse probability of treatment weighting; CBPS, covariate balancing propensity score; HR, hazard ratio; CI, confidence interval.
Anaemia is prevalent comorbidity in critically ill surgical patients, and we linked two databases and employed a propensity score approach to address the long-term mortality impact of anaemia.

We found that approximately one-third of critically ill surgical patients had anaemia within one week, and week-one anaemia correlated with an increased risk of one-year mortality. Our findings highlight the long-term mortality impact of anaemia and shed lights on the essential need of patient blood management program in critically ill surgical patients.

Data Availability
The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethical Approval
This study was approved by the Taichung Veterans General Hospital Ethics Review Committee (TCVGH: SE21098B) with the exemption of informed consent due to the analysed data were deidentified.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Authors’ Contributions
Study conception and design were carried out by F-HW, C-LW, and W-CC. Acquisition of data was carried out by L-TW, C-LW, and W-CC. Analysis and interpretation of data were carried out by L-TW and W-CC. Drafting of manuscript was carried out by F-HW and W-CC. All authors read and approved the final manuscript.

Acknowledgments
This study was supported by Veterans General Hospitals (Grant nos. TCVGH-1114402C, TCVGH-111G213, and VGHUST111-G2-1-3) and Ministry of Science and Technology Taiwan (Grant no. MOST 110-2321-B-075A-001). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary Materials
Table 1. Characteristics between the patients categorised by week-1 level of haemoglobin in the IPTW and CBPS cohort. (Supplementary Materials)
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