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The effect of anemia on the severity and prognosis of patients with acute pancreatitis

A single-center retrospective study

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Abstract

Anemia was a risk factor for a worse prognosis of many diseases. This study aims to investigate the relationship between anemia and the severity and prognosis of acute pancreatitis (AP). Inpatients hospitalized at the First Affiliated Hospital of Guangdong Pharmaceutical University with a primary diagnosis of AP between 1st July 2016 to 31st December 2020 were enrolled. Subsequently, disease severity, the incidence of complications, and the prognosis of patients with AP were compared between the anemic group and the non-anemic group. A total of 282 patients with acute pancreatitis were enrolled; 68.43% of them were also diagnosed with anemia. Notably, these patients had more severe disease (higher RANSON, acute physiologic assessment and chronic health evaluation-II, bedside index for severity in acute pancreatitis, and multiple organ dysfunction syndrome scores); higher incidence of organ failure (acute kidney injury [AKI] and acute heart failure); worse prognosis (higher incidence of vasoactive and diuretic agent use, longer hospital stays, and higher hospital costs) compared to that of patients without anemia (all $P < .05$). After adjusting for potential confounders, acute physiologic assessment and chronic health evaluation-II, bedside index for severity in acute pancreatitis, multiple organ dysfunction syndrome scores, hospital stay, and hospital costs in anemic patients were higher than those in non-anemic patients; besides, the incidence of AKI and using a diuretic agent in anemic patients was 6.645 and 4.053 times that of non-anemic patients in AP, respectively (all $P < .05$). Acute pancreatitis patients with anemia have more disease severity, higher incidence of AKI, and worse prognosis compared to those without anemia.

Abbreviations: AHF = acute heart failure, AKI = acute kidney injury, AP = acute pancreatitis, APACHE = acute physiologic assessment and chronic health evaluation, BISAP = bedside index for severity in acute pancreatitis, BUN = blood urea nitrogen, CTSI = computed tomography severity index, Hb = hemoglobin, MODS = multiple organ dysfunction syndrome, SIRS = systemic inflammatory response syndrome, WBC = white blood cell.

Keywords: acute kidney injury, anemia, hemoglobin, pancreatitis

1. Introduction

Acute pancreatitis (AP) is the autodigestion of the pancreas characterized by a local and systemic inflammatory response.[1,2] With a global incidence of about 34/100,000 person-years, AP is the most prevalent gastrointestinal disease, causing acute admission to the hospital and the 5th leading cause of in-hospital mortalities in the United States.[3,4] An estimated 20% of patients develop moderate or severe AP, taking a substantial mortality rate of 20% to 40% accompanied by severe complications including acute kidney injury (AKI), acute heart failure (AHF), and acute respiratory failure, whose mortality is 15% to 35%.[1,5]

Current studies indicate that identifying the severity of AP and developing appropriate treatment during the early stages can improve the prognosis of patients.[6,7] The ability to detect the severity of patients with AP early is of considerable clinical importance. Notably, several scoring systems exist for assessing the severity of AP, including acute physiologic assessment and chronic health evaluation (APACHE II), bedside index for severity in acute pancreatitis (BISAP), computed tomography severity index (CTSI), multiple organ dysfunction syndrome (MODS) and systemic inflammatory response syndrome (SIRS)[8]; however, these scoring systems require complex image logical examination or too much data making it cumbersome.[9–11] Therefore, it is necessary to identify a simple, convenient, and efficient marker that identifies the severity of AP and predicts AP-related complications.[12]

Of note, hemoglobin (Hb) is a routine laboratory indicator tested on admission. A recent study reported that hemoglobin

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

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level is related to the severity of COVID-19, that is, the lower the hemoglobin level, the more severe the COVID-19.[13] As an independent risk factor of numerous illnesses, anemia (Hb < 120 g/L for males or < 110 g/L for females) triggers a worse prognosis of gastric cancer and is associated with increased mortality in diffuse large B-cell lymphoma.[14–16] However, the relationship between anemia and severity and severe complications of AP remains unclear. This work aims to evaluate the relationship between anemia and the severity and prognosis of acute pancreatitis.

2. Materials and Methods

2.1. Ethical statement

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China (No. 2021-147). The requirement for informed consent was waived by the institutional review board due to the retrospective study design.

2.2. Participants

Inpatients hospitalized at the First Affiliated Hospital of Guangdong Pharmaceutical University with a primary diagnosis of AP between 1st July 2016 to 31st December 2020 were considered for this analysis. Patients with incomplete medical records, diagnosed with chronic pancreatitis, after organ transplantation, and pregnant patients were excluded.

2.3. Data collection

The following data were extracted from the electronic medical records of patients: Sex, age, smoking, alcoholism, hypertension, diabetes mellitus, interventions (including, tracheal intubation, pancreatic surgery, transfer to the intensive care unit), outcomes (including hospital cost, the hospital stay), and laboratory test results *at admission* (including Hb, red blood cell, thrombocyte, hematocrit, white blood cell (WBC), serum creatinine, blood urea nitrogen (BUN), and C-reactive protein).[17]

2.4. Definition

A diagnosis of AP was confirmed if a patient met 2 of 3 criteria: Suffers acute upper abdominal pain; Serum amylase or lipase or both greater than or equal to 3 times of the upper limit of normal; Discovers AP on imaging including abdominal CT, MRI, or ultrasound.[1] Anemia was defined as Hb less than 120 g/L in males or less than 110 g/L in females based on gender. Alcoholism was defined as drinking alcohol greater than 140 g per week. Diagnostic criteria for AKI was a reduction in renal function currently within 48 hours (serum creatinine increasing to ≥1.5 times of baseline, an increase in serum creatinine ≥ 26.4 μmol/L (or 0.3 mg/dL), or a reduction in urination (<0.5 mL/kg/hours more than 6 hours).[18] Notably, BISAP, CTSI, APACHE-II, RANSON, SIRS, and MODS are the scoring systems for assessing the severity of the disease.

2.5. Statistical analysis

The patients were divided into 2 groups (anemic group or non-anemic group) based on their Hb. The Shapiro–Wilk test was used to test the assumption of normality. To express the concentration and dispersion of data, quantitative data with median and IQR or mean ± SD, and categorical data with frequency and percentages (%) were described. Levene's test was applied to evaluate the homogeneity of quantitative data. Differences in quantitative data were assessed using the Mann–Whitney *U* test or Student's *t*-test, while the Chi-square test was used for categorical variables. Spearman correlation or Pearson correlation coefficients were used to expressing the relationship between 2 continuous data when the parametric test was not eligible. Stepwise, backward binary logistic regression and multiple linear regression analyses were used to determine independent predictors of severity in AP. Based on a study in GASTROENTEROLOGY, we adjusted for gender, age, Hb, WBC count, calcium, triglycerides, serum glucose.[17] Besides, all indicators with significant differences between the anemia group and the non-anemic group ($P < .05$) were included in the above multivariate analysis. All the data were analyzed using the SPSS software (25.0) (IBM Corporation, NY). All statistical tests were 2-tailed; $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

Based on strict inclusion and exclusion criteria in the analysis, 282 patients (89 anemic patients and 193 non-anemic patients) were finally enrolled. The general characteristics and comparison of each parameter between anemic and non-anemic groups are shown in Table 1.

3.2. Laboratory test results between the anemic group and non-anemic group

In contrast with patients in non-anemic group, patients in anemic group demonstrated significantly higher levels of serum creatinine (88.00 vs 70.00; $P = .001$) and BUN (7.20 vs 4.79; $P < .001$), and lower levels of Hb (99.00 vs 136.00; $P < .001$), red blood cell count (3.26 vs 4.41; $P < .001$), thrombocyte count (169.00 vs 208.00; $P = .003$), hematocrit (0.30 vs 0.40; $P < .001$), amylase (257.00 vs 427.00; $P = .005$), calcium (2.05 vs 2.13; $P = .002$), WBC count (8.16 vs 10.59; $P < .001$) and alanine transaminase (28.00 vs 41.00; $P = .042$) (Table 2).

Table 1

Acute pancreatitis patient characteristics.

Demographic	Non-anemia (n = 193)	Anemia (n = 89)	*P* value
Age (yr)	55.00 (43.50–72.00)	68.00 (47.00–82.00)	.003
Male (%)	115 (59.58)	46 (51.68)	.213
Alcoholism (%)	24 (12.44)	7 (7.87)	.254
Smoking (%)	48 (24.87)	16 (17.98)	.070
Hypertension (%)	67 (34.72)	34 (38.20)	.57
Diabetes mellitus (%)	36 (18.65)	21 (23.60)	.337
CCI	1.00 (0.00–2.00)	2.00 (1.00–3.00)	<.001

Data are median (interquartile range) or n (%).

CCI = Charlson comorbidity index.

Table 2

Laboratory values in hospital admission of acute pancreatitis patient.

Laboratory values	Non-anemia (n = 193)	Anemia (n = 89)	*P* value
Hb (g/L)	136.00 (125.00–148.00)	99.00 (73.50–109.00)	<.001
RBC ($\times 10^{12}$/L)	4.41 (4.00–4.82)	3.26 (2.50–3.71)	<.001
Thrombocyte ($\times 10^{9}$/L)	208.00 (166.00–261.50)	169.00 (111.00–248.00)	.003
Hematocrit	0.40 (0.37–0.43)	0.30 (0.23–0.33)	<.001
WBC ($\times 10^{9}$/L)	10.59 (7.51–14.12)	8.16 (5.44–11.92)	<.001
Amylase (U/L)	427.00 (211.50–915.50)	257.00 (152.75–522.75)	.005
Lipase (U/L)	381.60 (136.10–755.60)	297.95 (128.63–565.73)	.230
Triglyceride (mmol/L)	1.32 (0.80–3.56)	1.15 (0.71–1.99)	.134
Calcium (mmol/L)	2.13 (2.01–2.25)	2.05 (1.94–2.18)	.002
Serum glucose (mmol/L)	6.81 (5.45–10.00)	6.24 (5.13–8.89)	.105
ALT (U/L)	41.00 (20.75–150.00)	28.00 (13.00–121.00)	.042
AST (U/L)	42.50 (23.00–104.25)	41.00 (24.00–145.00)	.695
CRP (mg/L)	45.00 (8.85–122.65)	30.00 (17.63–90.03)	.809
SCr (μmol/L)	70.00 (57.50–86.50)	88.00 (59.00–201.00)	.001
BUN (mmol/L)	4.79 (3.57–6.57)	7.20 (4.92–16.99)	<.001

Data are median (interquartile range).

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CRP = C-reactive protein, Hb = hemoglobin, RBC = red blood cell, SCr = serum creatinine, WBC = white blood cell.

Table 3

Scoring systems and severe complications of acute pancreatitis.

Scoring systems	Non-anemia (n = 193)	Anemia (n = 89)	*P* value
RANSON	1.00 (1.00–2.00)	2.00 (1.00–2.00)	.004
APACHE II	6.00 (3.00–9.00)	11.00 (6.50–16.00)	<.001
BISAP	1.00 (0.00–2.00)	2.00 (1.00–3.00)	<.001
CTSI	2.00 (2.00–4.00)	4.00 (2.00–4.00)	.978
MODS	1.00 (0.00–1.50)	2.00 (0.50–4.00)	<.001
SIRS (%)	54 (27.98)	33 (37.08)	.124
AKI (%)	13 (6.74)	17 (19.10)	.002
AHF (%)	6 (3.11)	15 (5.32)	.021
ARF (%)	8 (4.15)	6 (6.74)	.382

Data are median (interquartile range) or n (%).

AHF = acute heart failure, AKI = acute kidney injury, APACHE II = acute physiologic assessment and chronic health evaluation, ARF = acute respiratory failure, BISAP = bedside index for severity in acute pancreatitis, CTSI = computed tomography severity index, MODS = multiple organ dysfunction syndrome, SIRS = systemic inflammatory response syndrome.

3.3. Scoring systems and severe complications of AP between the anemic group and non-anemic group

The RANSON (2.00 vs 1.00; $P = .004$), APACHE II (11.00 vs 6.00; $P < .001$), BISAP (2.00 vs 1.00; $P < .001$), MODS scores (2.00 vs 1.00; $P < .001$), the incidence of AKI (19.10% vs 6.74%; $P = .002$) and AHF (5.32% vs 3.11%; $P = .021$) of patients in anemic group were significantly higher than those in patients in non-anemic group (Table 3).

3.4. Interventions and outcomes of AP between anemic group and non-anemic

The percentage of using diuretic agents (28.10% vs 10.36%; $P < .001$) and vasoactive agents (7.87% vs 2.07%; $P = .045$) in the anemic group was significantly higher compared to that in the non-anemic group.

Besides, in contrast with patients in the non-anemic group, patients in the anemic group had a longer hospital stay (13.00 vs 9.00; $P = .006$) and incurred a higher hospital cost (32588.33 vs 20886.81; $P = .001$) (Table 4).

3.5. Correlation between hemoglobin and disease severity

A correlation analysis was performed between hemoglobin and disease severity indices and outcomes, respectively. Consequently, a mild and significant negative correlation was noted between hemoglobin and the disease severity indices, hospital stay, and hospital cost of AP (Table 5).

3.6. Multivariate analysis of anemia for the disease severity of acute pancreatitis

We adjusted for gender, age, anemia, WBC count, calcium, triglycerides, serum glucose, alanine transaminase, and amylase in a multivariate analysis regression model. All these parameters were entered as independent variables in multiple linear regression and binary logistic regression analyses. APACHE-II, BISAP, MODS, CTSI, and RANSON scores were entered as dependent variables in the multiple linear regression analysis, respectively. AKI, AHF, acute respiratory failure, and SIRS were entered as dependent variables in the binary logistic regression analysis, respectively.

Multiple linear regression model revealed that controlling other factors, APACHE-II score ($\beta = 0.297$; $P < .001$), BISAP score ($\beta = 0.304$; $P < .001$), MODS score ($\beta = 0.319$; $P < .001$), hospital stay ($\beta = 0.208$;$P = .003$) and the hospital cost ($\beta = 0.243$;$P = .001$) in anemic patients was significantly higher compared to that of non-anemic patients in acute pancreatitis (Table 6).

Binary logistic regression model showed that after adjusting for potential confounders, AKI incidence (OR = 6.645; 95% CI 2.252 to 19.604; $P = .001$), SIRS (OR = 3.346; 95% CI 1.353 to 8.274; $P = .009$) and using diuretic agent

Table 4

Interventions and outcomes of acute pancreatitis.

Intervention or outcome	Non-anemia (n = 193)	Anemia (n = 89)	*P* value
Hospital stay (d)	9.00 (6.00–13.00)	13.00 (7.50–17.00)	.006
Hospital expenses (yuan)	20886.81 (14017.67–38957.66)	32588.33 (20432.46–48911.18)	.001
Using **diuretic** agent (%)	20 (10.36)	25 (28.10)	<.001
Using vasoactive agent (%)	4 (2.07)	7 (7.87)	.045
Tracheal intubation (%)	0 (0.00)	2 (2.25)	.099
Pancreatic surgery (%)	0 (0.00)	2 (2.25)	.100
Transferred to the intensive care unit (%)	2 (1.04)	3 (3.37)	.371

Data are median (interquartile range) or n (%).

Table 5

Correlation between hemoglobin and disease severity.

Scoring systems	*r*	*P* value
RANSON	–0.232	<.001
APACHE II	–0.478	<.001
BISAP	–0.349	<.001
CTSI	0.084	.161
MODS	–0.326	<.001
CCI	–0.272	<.001
Hospital stays (d)	–0.196	.001
Hospital costs (yuan)	–0.216	<.001

APACHE II = acute physiologic assessment and chronic health evaluation, BISAP = bedside index for severity in acute pancreatitis, CCI = Charlson comorbidity index, CTSI = computed tomography severity index, MODS = multiple organ dysfunction syndrome.

Table 6

Multiple linear regression analysis of anemia for disease severity in acute pancreatitis.

Model	Adjusted R^2	β	*P* value
APACHE-II**	0.371	0.297	<.001
BISAP**	0.448	0.304	<.001
CTSI**	0.255	–	–
Ranson**	0.502	–	–
MODS**	0.214	0.318	<.001
Hospital stays**	0.160	0.208	.003
Hospital costs**	0.150	0.243	.001

We adjust for gender, age, anemia, white blood cell count, calcium, triglycerides, serum glucose, alanine aminotransferase, and amylase.

APACHE II = acute physiologic assessment and chronic health evaluation, BISAP = bedside index for severity in acute pancreatitis, CTSI = computed tomography severity index, MODS = multiple organ dysfunction syndrome.

**Means model $P \leq .001$.

(OR = 4.053; 95% CI 1.772 to 9.268; $P = .001$) in anemic patients was 6.645 times, 3.346 times and 4.053 times that of non-anemic patients in acute pancreatitis, respectively (Table 7).

4. Discussion

In the present study, 68.43% of patients with AP were also diagnosed with anemia. These patients developed an increasingly severe disease (higher RANSON, APACHE-II, BISAP, and MODS scores), higher incidence of organ failure (AKI and AHF), and worse prognosis (higher incidence of use of vasoactive agent and diuretic agent, longer hospital stays, and higher hospital costs) compared to those without anemia. Thus, identifying whether AP patients have anemia help clinicians select appropriate therapeutic interventions, prevent organ failure and improve prognosis.

We found that disease severity scores in AP patients with anemia were significantly higher than those in patients without anemia. Similar results were reported in a previous study, where the severity prediction score (including Hb and BUN) recognized patients developing the severe disease with an 81.5% sensitivity.[19] Moreover, anemia-related markers including red blood cell distribution width and nucleated red blood cells positive rate in peripheral blood were associated with the mortality of AP.[20–22] Numerous studies have shown that anemia is associated with disease severity of other diseases. A recent study from El-Obour Ain Shams University Isolation Hospital revealed that Hb level correlates with COVID-19 disease severity; the lower the Hb level, the increasingly severe the disease.[13] Besides, a meta-analysis, which enrolled 4,20,970 chronic obstructive pulmonary diseases patients identified that patients with anemia showed a more severe disease than those without anemia.[23] The following suggestions may explain why anemia is associated with the severity of AP. First, AP is a systemic inflammatory disease, accompanied by the production of multiple inflammatory cytokines[1]; moreover, AP patients with severe disease may have colossal inflammatory cytokines in their blood.[24] These cytokines limit iron absorption in the intestinal, reduce erythropoietin production, and inhibit erythrocyte maturation, thereby resulting in anemia.[25] In turn, anemia reduces the oxygen-carrying capacity of the blood leading to organ hypoxia,[15] which may aggravate the disease severity of AP. As such, anemia is a potential indicator in evaluating the disease severity of AP.

Furthermore, this paper discovered that the incidence of AKI and AHF in the anemic group are significantly higher than those in the non-anemic group; also, anemia is an independent risk factor for the development of AKI after adjusting for other factors. Similar results have been reported in several previous studies. A recent study demonstrated that the risk of rapid decline in kidney function in patients with anemia was 64% higher than that in patients without anemia.[26] Coincidently, a study that enrolled 439 chronic kidney disease patients revealed that a decrease of eGFR was significantly faster in anemic patients than that in non-anemic participants.[27] Additionally, Meguro et al found that Hb concentration is a vital factor for renal deterioration in patients with type 2 diabetes mellitus.[28] Notably, the mechanism of a drop in kidney function among patients with anemia may be related to renal ischemia and hypoxia. Previous studies indicate that approximately 18% to 28.6% of patients with severe AP were accompanied by gastrointestinal bleeding, based on stress gastric mucosal injury, peptic ulcer, formation of pseudoaneurysms, etc.[29–31] Gastrointestinal bleeding reduces renal perfusion pressure and blood oxygen-carrying capacity, leading to renal ischemia and hypoxia, hence AKI.[32,33] In addition, we found that the incidence of using of diuretic agents in the anemia group was higher than that in the non-anemia group; this was attributed to the higher incidence of AKI in the anemic group. Therefore, when AP patients are diagnosed with anemia, clinicians should look out for AKI incidence then provide adequate and timely fluid resuscitation to improve renal perfusion.

Table 7

Binary logistic regression analysis of anemia for disease severity and interventions in acute pancreatitis.

Model	R^2	OR (95% CI)	*P* value
AKI*	0.175	6.645 (2.252–19.604)	.001
AHF*	0.356	–	–
ARF*	0.251	–	–
SIRS*	0.349	3.346 (1.353–8.274)	.009
U**sing diuretic** agent*	0.197	4.053 (1.772–9.268)	.001
Using vasoactive agent *	0.285	–	–
Tracheal intubation*	1.000	2.378E57 (–)	.966
Pancreatic surgery*	1.000	1.398E57 (–)	.972
Transferred to the intensive care unit *	0.146	–	–

We adjust for gender, age, anemia, white blood cell count, calcium, triglycerides, serum glucose, alanine aminotransferase, and amylase.

AHF = acute heart failure, AKI = acute kidney injury, ARF = acute respiratory failure, CI = confidence interval, SIRS = systemic inflammatory response syndrome.

*Means model $P \leq .05$.

Besides, AP patients combined with anemia had longer hospital stays and incurred higher hospital costs. Similar results have been reported in many previous studies on other diseases. Research has shown that inflammatory bowel disease patients with anemia had higher hospital costs,[34,35] and anemic patients in chronic obstructive pulmonary diseases, radiation enteritis, and perioperative patients had longer hospital stays.[36–39] A prospective, multicenter study found that Hb < 90g/L is a risk factor for prolonged hospital stays in critical patients at the intensive care unit.[40] Among patients with AP disease, Shen et al revealed a significantly increased mortality of AP patients with gastrointestinal bleeding.[30,31] Gastrointestinal bleeding causes anemia in varying degrees; this may explain why AP patients with anemia had a worse prognosis. Simultaneously, we found that AP patients with anemia had a higher incidence of using diuretic agents and vasoactive drugs. Also, the hospital costs of AP patients with anemia were higher than that of non-anemic patients; this may be associated with longer hospital stays, the more severe the disease, the more complications, and thus the need for additional drug interventions in anemic patients. Additionally, several lines of evidence indicate that anemia triggers a worse prognosis for gastric cancer, diffuse large B cell lymphoma, and radioactive enteritis.[15,16,37] Generally, anemia worsens the prognosis of patients, therefore, clinicians should identify anemic patients and provide timely therapy interventions, hence improving the prognosis of AP patients.

The major limitation of this work is its retrospective design; besides, a few confounding factors which would influence the severity of disease were missing, including the time from disease onset to hospitalization and other underlying diseases, hence introducing bias to the results. Secondly, clinical data including erythropoietin, serum iron, transferrin levels, and transferrin saturation rate were missing, hence, further analysis for anemic types could not be conducted. Thirdly, our study used a small sample size and is a single-center study. Thus, our findings should be validated by prospective, and multicenter studies with a large sample size.

5. Conclusion

In conclusion, AP patients with anemia develop increasingly disease severity, higher AKI incidence, and worse prognosis compared to those without anemia. Therefore, a possible diagnosis of anemia should be checked among AP patients at admission; besides, timely identification of severe patients, measurement of the kidney function marks, including serum creatinine, blood urea nitrogen, and urine volume should be performed. This will indicate the occurrence of AKI, and therefore timely and appropriate therapeutic measures should be implemented to improve the prognosis.

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