



Original Article

Group-Based Trajectory Modeling of Platelet in Patients with Aplastic Anemia: A Study Based on the MIMIC Database

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Abstract. Background: Platelets are the main components supporting coagulation and hemostasis. Nevertheless, no sufficient research has been done on how variations in platelet counts during hospital stays affect aplastic anemia (AA) patients' prognoses.

Objective: This study proposes to evaluate the association between alterations in platelet levels and illness risk in patients with AA using group-based trajectory modeling (GBTM).

Methods: GBTM was used to group AA patients based on changes in platelet levels. Cox regression models were used to evaluate the relationship between platelet levels and patients' 30-day survival status. Kaplan-Meier (K-M) survival curve analysis was used to assess the impact of platelet transfusion on survival among different trajectory groups of patients.

Results: Three trajectory patterns were recognized by GBTM: Class 1, Class 2, and Class 3. Even after controlling for confounding variables, the Cox risk estimates showed that AA patients had a higher chance of surviving in Class 1 (OR>1, P<0.05). Class 2 patients had the greatest survival, according to K-M (Log-rank P<0.001). According to landmark research, Class 1 patients' survival was not improved by platelet transfusion.

Conclusion: Patients with AA who had increasing platelet trajectories during their hospital stay had a higher 30-day survival rate; hence, patients with low platelet counts might not be good candidates for platelet transfusion treatment.

Keywords: Aplastic anemia; GBTM; MIMIC-IV; Platelets.

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Introduction. Reduced blood cells and/or nonexistent hematopoietic precursors in the bone marrow are the results of the uncommon, life-threatening chronic primary hematological failure disease known as aplastic anemia (AA).¹ This condition is caused by the death of hematopoietic stem cells in the bone marrow. The prevalence of AA is 2-3 times greater in Asia than in

Western countries, making it more frequent in developing nations.²⁻⁴ AA poses a considerable risk of mortality due to its progressive course and consequences from poor therapy; if definitive treatment is not received, the leading causes of death in severe AA over two years are bleeding and infection.^{5,6}

Treatment for hard-to-treat anemias such as AA,

myelodysplastic syndromes, and thalassemia can be achieved quickly, directly, and effectively with transfusion support of red blood cells and platelets.⁷⁻⁹ Through blood transfusions, the use of antibiotics, hematopoietic stem cell transplantation, or immunosuppressive medication, AA can reduce the emergence of anemia and thrombocytopenia-related symptoms, avoid severe infections and bleeding, and restore hematopoiesis.⁹ On the other hand, patients' quality of life is negatively impacted by long-term blood transfusion assistance, and receiving platelets repeatedly can result in refractory platelets, which is linked to a bad prognosis for patients and a considerable rise in hospitalization expenses.^{10,11} However, the effects of high-volume, long-term platelet transfusions on patients with AA are the only things that trials can currently show. The associations between platelet dynamic levels during transfusion therapy and curative treatment and the clinical results of AA remain unresolved, and little study has been done on the subject.

A well-developed analytical technique that may identify the quantity and features of individual trajectory clusters with comparable result progressions across time is the group-based trajectory model (GBTM). It has been extensively utilized in medical research and offers flexible and low-bias estimations of trajectory curves.¹² Thus, the goal of this study was to create a GBTM to investigate the clinical and demographic characteristics linked to each unique trajectory and to determine, for the first time, the correlation between diagnostic platelet level changes and survival rates in patients with AA. This approach aids in figuring out how trajectories and associated elements influence treatments that are

motivated for further study.

Methods

Data sources. The Institutional Review Board of the Beth Israel Deaconess Medical Center (BIDMC), Boston, Massachusetts, USA, developed the MIMIC-IV (Medical Information Mart for Intensive Care), from which the data were taken.¹³ A major resource for studying critical care outcomes, predictive modeling, clinical decision support, and other research fields, MIMIC-IV is a publicly accessible critical care database that is well-known for its vast clinical data on patients treated in the intensive care unit (ICU). This data includes patient demographics, vital signs, medicines, laboratory measures, fluid balances, procedural and diagnostic codes, imaging reports, duration of stay, and fatalities (<https://mimic.physionet.org/about/mimic/>). MIT and BIDMC granted permission for this study to access the MIMIC-IV database.

Patient selection. Clinical information for 299,712 ICU patients hospitalized between 2008 and 2019 is available in the MIMIC-IV database. Of these, 7,079 individuals had ICD-9 and ICD-10 codes (ICD-9: 284, ICD-10: D60 and D61) that indicated they had AA. We only included patients who were 18 years of age or older in our study, and we gathered information from their first ICU stay. Patients who had daily platelet measurement records less than 4 times, had non-first ICU admission and had ICU stays shorter than 24 hours were among the exclusion criteria. Consequently, the final analysis comprised 398 patients in total (**Figure 1**).

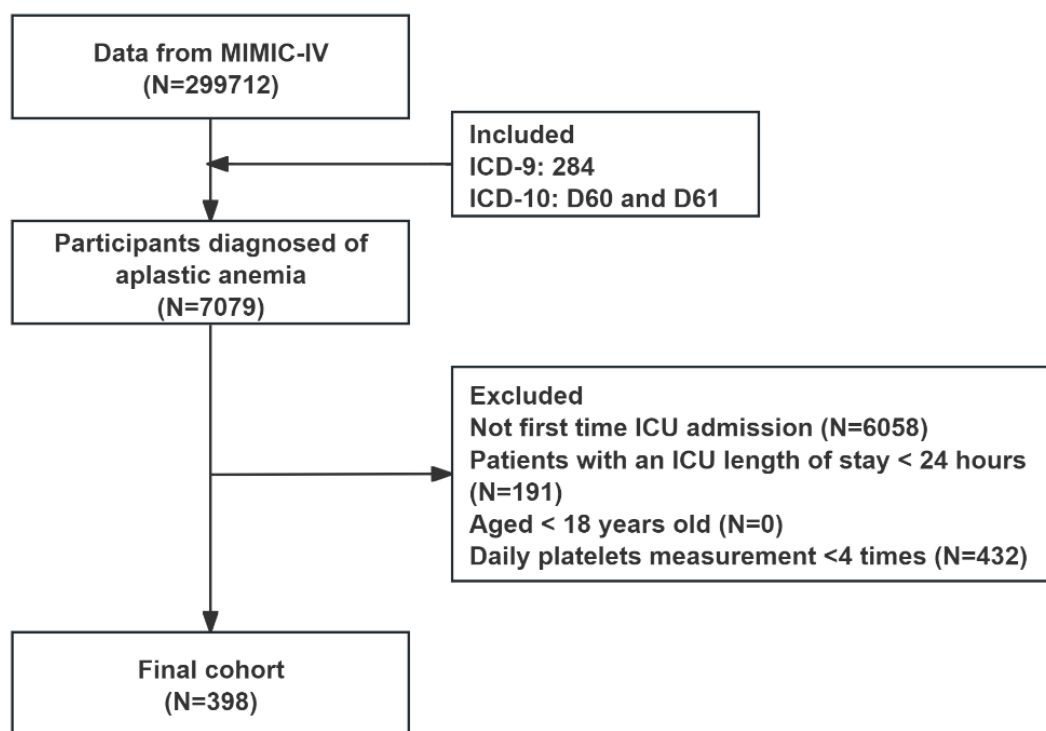


Figure 1. A flowchart for the patient selection process.

Variable collection. With the aid of Structured Query Language (SQL), all variables were taken out of the MIMIC-IV database. Vital signs, laboratory testing, demographics, clinical characteristics, and comorbidities are the five primary components of the extraction process. Only variables with missing proportions of less than 20% are considered for additional analysis. The 30-day ICU survival rate—which measures the amount of time from ICU admission to the study's conclusion—was the main result of this investigation. Throughout the first week following ICU admission, the daily platelet measurement values served as the independent variable. The measurement outcome should be the lowest platelet value obtained from a patient undergoing several platelet tests in a single day. Initial baseline characteristics and laboratory results measured within 48 hours of ICU admission were recorded and analyzed (**Table S1**).

Platelet trajectory grouping. To convert diverse populations into homogenous groups with comparable trajectories, populations with similar developmental trajectories of platelet levels were identified using the Group-based Trajectory Model (GBTM) approach. Trajectories were identified and determined using GBTM and the 'lcmm' package. Patients were categorized into three groups using the GBTM approach according to platelet counts obtained during the first week of ICU hospitalization. The precise procedure is building a polynomial model devoid of variables to ascertain the number of groups. The Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC), the Sample-size adjusted BIC (SABIC), entropy, and the ratio of samples in each trajectory group to the overall sample were used to identify the best-fitting model.

Propensity score matching. The procedure of selecting patients for retrospective research has inherent constraints that might cause bias and introduce confounding variables. We performed Propensity Score Matching (PSM) analysis to reduce the influence of bias and confounding variables to solve these problems. Propensity scores are determined by PSM analysis by building a logistic regression model, which is subsequently utilized to match patients based on many characteristics. The variables used to calculate propensity scores include age, gender, race, marital status, length of stay (LOS), ICU mortality rate, heart rate, weight, mean systolic blood pressure (MBP), respiratory rate, temperature, peripheral blood oxygen saturation (SpO₂), blood glucose, urine output, Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), anion gap (AG), bicarbonate, chloride, hematocrit, hemoglobin, potassium, partial thromboplastin time (PTT), international normalized ratio (INR), prothrombin time (PT), blood calcium,

blood sodium, white blood cell count (WBC), red blood cell count (RBC), creatinine, blood urea nitrogen (BUN), alkaline phosphatase (ALP), aspartate transaminase (AST), bilirubin, mechanical ventilation, renal replacement therapy (RRT), antidiuretic hormone, antiplatelet drug use, antibiotic use, platelet transfusion, red blood cell transfusion, congestive heart failure, peripheral vascular disease, chronic lung disease, acute kidney injury (AKI), sepsis, kidney disease, liver disease, diabetes, multiple myeloma, leukemia, lymphoma. PSM analysis used a 1:1 nearest neighbor matching algorithm with a caliper of 0.1.

Statistical analysis. The Wilcoxon-Mann-Whitney test was utilized to evaluate the differences between groups, and continuous variables were displayed as the median (IQR). The chi-square test was used to compare categorical variables, which were shown as percentages (%). A two-sided P value < 0.05 was considered statistically significant. The baseline table compared the differences in baseline characteristics among patients with different platelet trajectory groups. To examine the relationship between various trajectories and the 30-day survival status in AA patients, Kaplan-Meier (K-M) curves were created, adjusted for confounding variables, and used to evaluate the survival disparities across various groups. The survival status of AA patients was then assessed using K-M curves at various intervals following red blood cell and platelet transfusions between groups both before and after PSM. Cox proportional risk models were used to study groups with varying platelet trajectories to ascertain the impact of platelet levels on the 30-day survival status in patients with AA. In this work, R (Version 4.2.3) was used for data analysis after SQL was used to gather data from the MIMIC-IV (Version 2.2) database. The R packages included tableone, mice, glm, MatchIt, jskm, and survival. The 'mice' package was used to impute missing values using the Random Forest (RF) method.

Results

Characterization of platelet trajectories. **Table 1** displays the model performance of GBTM trajectory modeling of platelet variations for 7 days following ICU admission. We integrated many criteria, including AIC, BIC, and SABIC, and conducted multiple fits on the polynomial. For the following analysis, we employed a quadratic model with three groups, Class 1, Class 2, and Class 3, accounting for 58.54%, 34.67%, and 6.78%, respectively.

Figure 2 and **Table 2** display the platelet changes throughout one week. Class 1 kept its low platelet count steady. Platelet counts in Class 2 indicated an upward trend. Class 3 started with a higher baseline platelet count, followed by a decrease and then an increase with significant fluctuations. The platelet counts of the

Table 1. Fit statistics for different term and number of trajectory groups

Classes	Log likelihood	AvePP	AIC	BIC	SABIC	entropy	%class1	%class2	%class3	%class4	%class5	%class6
Cubic												
1	-17335.41		34680.81	34700.74	34684.88	1.00	100.00					
2	-16674.13	0.9918, 0.9676	33368.25	33408.12	33376.39	0.97	87.44	12.56				
3	-16334.83	0.9651, 0.9535, 0.9959	32699.66	32759.45	32711.86	0.92	56.78	36.93	6.28			
4	-16000.60	0.9698, 0.9687, 0.9966, 0.9954	32047.20	32138.88	32065.90	0.95	34.42	58.29	4.02	3.27		
5	-15766.29	0.9742, 0.9801, 0.9362, 0.9967, 0.9998	31582.57	31682.23	31602.91	0.95	52.51	4.52	36.68	3.77	2.51	
6	-15644.07	0.9757, 0.9405, 0.8763, 0.9644, 1.000, 0.9718	31348.15	31467.74	31372.55	0.95	52.26	34.42	2.76	4.77	3.27	2.51
Quadratic												
1	-17335.55		34679.11	34695.05	34682.36	1.00	100.00					
2	-16678.62	0.9924, 0.9755	33373.25	33405.14	33379.76	0.97	87.44	12.56				
3	-16264.36	0.9613, 0.9594, 0.9764	32552.71	32600.55	32562.47	0.92	58.54	34.67	6.78			
4	-15999.52	0.973, 0.9625, 0.9906, 0.9986	32031.05	32094.83	32044.06	0.95	56.28	35.93	4.27	3.52		
5	-15812.13	0.9767, 0.9348, 0.9887, 0.9425, 0.9993	31664.27	31744.00	31680.54	0.94	51.51	36.93	4.52	5.03	2.01	
6	-15729.57	0.9398, 0.8532, 0.8978, 0.9914, 0.9966, 0.9999	31507.13	31602.81	31526.65	0.89	42.46	23.62	23.37	4.27	4.27	2.01
Linear												
1	-17338.94		34683.89	34695.85	34686.33	1.00	100.00					
2	-16686.44	0.9932, 0.9841	33384.88	33408.80	33389.76	0.97	87.69	12.31				
3	-16285.21	0.9624, 0.9626, 0.9634	32588.43	32624.31	32595.75	0.92	59.30	33.67	7.04			
4	-16012.01	0.9694, 0.9462, 0.9865, 0.9993	32048.02	32095.85	32057.78	0.94	53.02	36.68	5.03	5.28		
5	-15824.23	0.9456, 0.9780, 0.9720, 0.9684, 0.9998	31678.47	31738.26	31690.67	0.95	36.93	52.26	4.77	4.77	1.26	
6	-15733.08	0.9611, 0.9974, 1.000, 0.8853, 0.8773, 0.9992	31502.15	31573.91	31516.79	0.90	45.48	3.02	2.01	18.59	27.14	3.77

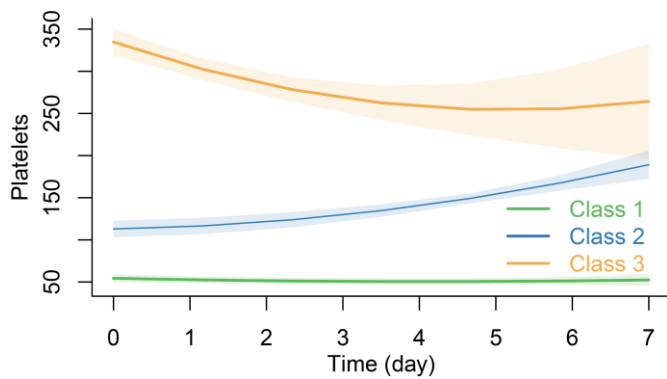


Figure 2. Three trajectories of the platelets based on GBTM. Shaded parts represent 95% CI, and the solid lines represent predicted values.

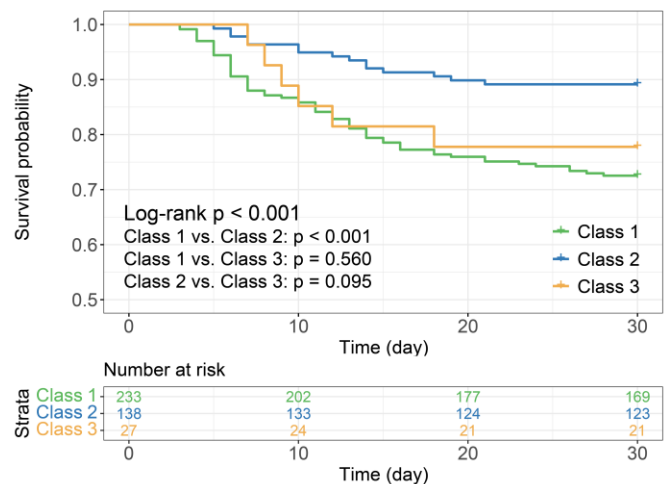


Figure 3. Survival curves show the association between the classes and 30-day mortality.

Table 2. Predicted values of three trajectories based on GBTM (Quadratic model)

Class	1	2	3	4	5	6	7	mean(sd)
1	54.39	52.51	51.25	50.62	50.61	51.22	52.46	51.87(1.36)
2	112.93	116.56	123.82	134.71	149.22	167.36	189.12	141.96(28.26)
3	334.68	302.40	278.34	262.50	254.87	255.47	264.29	278.93(29.64)

various groups varied significantly ($P < 0.001$, **Figure S1**).

Basic characteristics of trajectory grouping. **Table 3** displays clinical features and population demographics categorized by platelet trajectory. The differential analysis results of the three trajectory groups showed that the Class 1 group had significantly higher age, ICU mortality rate, SOFA score, INR, PT, creatinine, BUN, platelet transfusion ratio, red blood cell transfusion ratio, as well as proportions of sepsis and liver disease compared to the other two groups ($P < 0.05$), while MBP, hematocrit, hemoglobin, and RBC count were significantly lower ($P < 0.05$). Additionally, patients in Class 3 had significantly higher LOS, WBC, and potassium levels ($P < 0.05$). In terms of urine output, the highest value was in Class 2, at 2186.84 ± 1621.20 mL.

Platelet trajectories and survival rates. **Figure 3** displays the 30-day survival status Kaplan-Meier curve for AA patients in various classes. It showed substantial variations in the 30-day survival rates across the trajectory groups, with Class 2 patients having the greatest survival rate (Log-rank $P < 0.001$). Except for Class 1 and Class 2 (Log-rank $P < 0.001$), there was no significant difference in the comparison between any of the two groups (Log-rank $P > 0.05$) (**Figure 3**).

Cox proportional hazards regression analysis of platelet trajectories and 30-day survival status of AA patients. Cox models were built based on baseline platelet levels and various groups of platelets GBTM to investigate the

relationship between platelet trajectories and the 30-day survival status of AA patients. The 30-day survival status of AA patients did not significantly correlate with baseline platelet counts, according to the data ($P > 0.05$, **Table S2**). The GBTM results showed that Class 1 with stable low platelets had a considerably higher prognosis risk than Class 2 with continually increasing platelets. This link persisted even after adjusting for confounding variables ($P < 0.05$, **Table 4**).

The impact of platelet transfusion before and after PSM on the 30-day survival rate of AA patients. We also looked at how platelet transfusion affected patients in the lower platelet group (Class 1) in terms of their 30-day survival status (**Figure 4**). Long-term platelet transfusion significantly impacted patient survival in the original model prior to PSM, and this was linked to a decline in the survival rate of AA patients (log-rank $P < 0.001$, **Figure 4A**). However, after using PSM to account for confounding factors, the significance vanished (log-rank $P = 0.059$, **Figure 4B**). Platelet transfusion did not increase the survival of patients with low platelet counts (Class 1 group), and it may have a negative long-term impact on their survival, according to landmark analysis (log-rank $P = 0.035$, **Figure 4C**).

Discussion. Patients with AA had their platelet counts monitored throughout time, and the findings of these measurements were used to stratify the patients into three groups. It was discovered that a higher 30-day survival rate was related to the platelet levels in the Class 2 group

Table 3. Participants characteristics of included patients stratified by trajectory grouping for the GBTM analysis.

Characters	Class 1 N=233 (58.5)	Class 2 N=138 (34.7)	Class 3 N=27 (6.8)	p value
Gender				0.119
Female	98 (42.1)	69 (50.0)	16 (59.3)	
Male	135 (57.9)	69 (50.0)	11 (40.7)	
Age(years)	63.77 (14.24)	58.14 (17.59)	58.26 (18.72)	0.002
Race				
White	142 (60.9)	102 (73.9)	13 (48.1)	0.021
Black	11 (4.7)	7 (5.1)	3 (11.1)	
Other race	80 (34.3)	29 (21.0)	11 (40.7)	
Marital status				0.680
Married	94 (40.3)	51 (37.0)	9 (33.3)	
Unmarried	139 (59.7)	87 (63.0)	18 (66.7)	
LOS (day)	6.14 (6.40)	4.73 (4.84)	8.41 (14.65)	0.019
ICU mortality	64 (27.5)	15 (10.9)	6 (22.2)	0.001
Weight (kg)	79.62 (22.59)	82.51 (30.21)	71.70 (16.74)	0.115
Heart rate (times/min)	89.12 (16.55)	89.39 (17.23)	92.44 (19.06)	0.630
MBP (mmHg)	75.25 (10.32)	79.87 (12.73)	78.44 (10.72)	0.001
Breath rate (times/min)	20.15 (4.68)	20.27 (4.53)	20.85 (3.90)	0.747
Temperature (°C)	36.88 (0.60)	37.00 (0.54)	37.01 (0.61)	0.108
SpO2	96.81 (2.03)	96.92 (1.86)	96.63 (2.35)	0.756
Glucose (mg/dL)	471.45 (5037.80)	132.59 (44.31)	139.99 (38.47)	0.691
Urine output (mL)	1764.82 (1118.93)	2186.84 (1621.20)	1651.37 (1076.93)	0.007
GCS	13.70 (2.40)	13.81 (2.66)	13.74 (2.31)	0.909
SOFA	7.81 (3.58)	5.12 (3.36)	4.63 (2.92)	<0.001
Anion gap (mmol/L)	16.59 (4.84)	16.33 (4.12)	16.04 (5.56)	0.774
Bicarbonate (mmol/L)	20.45 (4.71)	20.96 (4.77)	21.32 (4.95)	0.462
Chloride (mmol/L)	105.54 (6.75)	105.47 (6.03)	104.89 (10.30)	0.895
Hematocrit (μmol/L)	25.34 (5.67)	27.93 (5.65)	28.96 (6.13)	<0.001
Hemoglobin (g/dL)	8.46 (1.91)	9.32 (2.02)	9.42 (1.90)	<0.001
Potassium (K/μL)	4.48 (0.81)	4.38 (0.87)	4.84 (1.03)	0.036
PTT (s)	40.43 (24.37)	42.04 (30.70)	51.55 (42.36)	0.151
INR	1.85 (1.50)	1.40 (0.53)	1.54 (0.65)	0.002
PT (s)	19.23 (12.25)	15.41 (5.51)	16.39 (6.60)	0.002
Calcium (mg/dL)	8.27 (0.84)	8.27 (0.77)	8.21 (0.73)	0.926
Sodium (mEq/L)	139.00 (5.57)	138.78 (4.94)	137.67 (10.27)	0.524
WBC (K/μL)	8.70 (14.30)	7.40 (6.20)	16.09 (22.95)	0.007
RBC (m/μL)	2.75 (0.65)	3.07 (0.74)	3.32 (0.71)	<0.001
Creatinine (mg/dL)	1.88 (2.04)	1.46 (1.39)	1.26 (0.88)	0.038
BUN (mg/dL)	37.63 (30.70)	28.00 (24.31)	34.89 (47.84)	0.013
ALP (IU/L)	136.92 (127.94)	128.22 (116.07)	147.67 (172.67)	0.703
AST (IU/L)	299.61 (996.52)	303.17 (1361.55)	116.59 (187.04)	0.706
Bilirubin (mg/dL)	2.99 (4.66)	2.07 (4.00)	1.79 (4.30)	0.097
Mechanical ventilation	84 (36.1)	38 (27.5)	14 (51.9)	0.033
RRT	11 (4.7)	1 (0.7)	0 (0.0)	0.060
Vasopressin	15 (6.4)	2 (1.4)	1 (3.7)	0.080
Anti-platelet drug usage	51 (21.9)	42 (30.4)	9 (33.3)	0.121
Antibiotic usage	197 (84.5)	103 (74.6)	22 (81.5)	0.063
Platelet transfusion	111 (47.6)	15 (10.9)	2 (7.4)	<0.001
Red blood cell transfusion	135 (57.9)	43 (31.2)	7 (25.9)	<0.001

Congestive heart failure	60 (25.8)	24 (17.4)	11 (40.7)	0.020
Peripheral vascular disease	15 (6.4)	9 (6.5)	0 (0.0)	0.395
Chronic pulmonary disease	51 (21.9)	34 (24.6)	7 (25.9)	0.780
AKI	195 (83.7)	102 (73.9)	24 (88.9)	0.037
Sepsis	155 (66.5)	67 (48.6)	14 (51.9)	0.002
Renal disease	59 (25.3)	23 (16.7)	5 (18.5)	0.136
Liver disease	95 (40.8)	36 (26.1)	7 (25.9)	0.010
Diabetes	63 (27.0)	29 (21.0)	6 (22.2)	0.410
Multiple myeloma	6 (2.6)	3 (2.2)	0 (0.0)	0.693
Leukemia	13 (5.6)	5 (3.6)	0 (0.0)	0.343
Lymphoma	22 (9.4)	8 (5.8)	1 (3.7)	0.320

MBP, mean blood pressure; GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell; RBC, red blood cell; PTT, partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; RRT, renal replacement therapy; AKI, acute kidney injury.

Table 4. Associations between different GBTM classes and hazard ratios (95% confidence intervals) for 30-day mortality

Outcomes	Class 2	Class 1	p	Class 3	p
Model 1	1.0 (ref.)	2.810 (1.601-4.930)	<0.001	2.185 (0.848-5.631)	0.106
Model 2	1.0 (ref.)	2.489 (1.410-4.395)	0.002	2.141 (0.823-5.570)	0.119
Model 3	1.0 (ref.)	2.118(1.032-4.348)	0.041	0.689 (0.154-3.076)	0.626

Model 1 was unadjusted. Model 2: adjust for age, gender, race and marital status. Model 3: model 2 plus adjustment for LOS, weight, Glasgow Coma Scale, SOFA, hematocrit, hemoglobin, platelets, WBC, BUN, creatinine, RBC, INR, PT, PTT, ALP, AST, bilirubin, spO₂, urine output, glucose, heart rate, MBP, breath rate, temperature, mechanical ventilation, vasopressin, antibiotic usage, anti-platelet usage, leukemia, lymphoma, and multiple myeloma

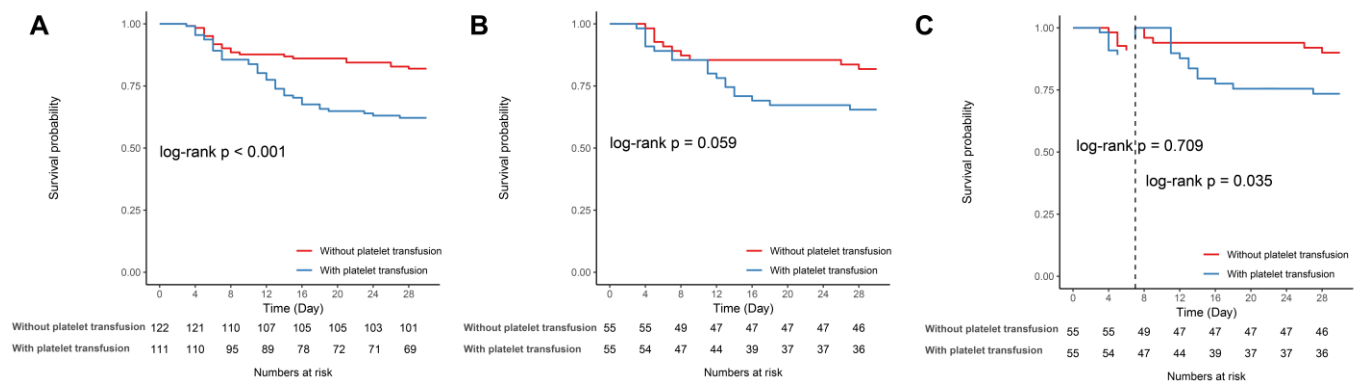


Figure 4. Kaplan-Meier curves of survival probability grouped by platelet transfusion in Class 1. A-B: Kaplan-Meier curves before and after PSM; C: Landmark survival analysis after PSM.

of AA patients. Following PSM adjustment, the data revealed that platelet transfusion had no significant benefits for survival in the group of AA patients with low platelet levels (Class 1), and it may even be detrimental to long-term survival.

AA is a rare autoimmune-mediated life-threatening bone marrow disease, primarily classified into congenital and acquired forms. The main pathogenic mechanisms of acquired AA involve abnormal activation of T lymphocytes and hyperfunction of bone marrow damage, leading to marrow destruction.^{14,15} This destruction is mediated by cytotoxic T cells, which target hematopoietic cells and hematopoietic stem and progenitor cells (HSPCs) through autoimmune attacks.

By secreting perforin and granzyme B to create pro-inflammatory cytokines such as interferon (IFN)- γ , tumor necrosis factor α , and through the Fas/Fas ligand pathway, activated cytotoxic T lymphocytes (CTLs) kill hematopoietic stem cells (HSPCs) and limit the development of blood cells and immune cells in adult hematopoiesis.^{14,16} The length of leukocyte telomeres resembles that of other somatic cells and is linked to the risk of illness associated with decreased cell proliferation and tissue deterioration.¹⁷ Telomeres are DNA components that are entangled with cell division. The naturally occurring enzyme telomerase helps to protect telomere length to some degree. However, mutations in telomerase components can result in inadequate telomere

maintenance in hematopoietic stem cells (HSCs), which can lead to bone marrow hypoplasia and premature HSC depletion.¹⁸ In acquired AA, telomere shortening may be a marker of bone marrow damage. Before allogeneic HSC transplantation, almost one-fifth of AA patients were found to have shorter telomere lengths, which is linked to the severity of AA, the risk of recurrence, and overall survival.¹⁹ This study did not analyze telomere length; therefore, we suggest that future research could further explore the role of telomere length in the etiology of AA, particularly in the context of distinguishing between acquired and congenital AA.

Survival was highest in the Class 2 trajectory group, which had a consistent trend of increasing platelet levels over a range of levels, compared with the other two trajectory groups. As components of bone marrow cells, platelet count and erythrocyte count are major predictors of peripheral blood stem cell mobilization in healthy donors and play a key role in physiological hemostasis and thrombosis.^{20,21} Surprisingly, we found that platelet transfusion did not provide additional survival benefits for AA patients with low platelet levels and even harmed long-term outcomes. In clinical practice, platelet transfusion is a routine supportive therapy used to treat bleeding and thrombocytopenia following hematopoietic stem-cell transplantation (HSCT) in accordance with pre-conditioning regimens.²² However, it is not long-term successful. Repetitive exposure to platelets can trigger alloimmune responses against Human Leukocyte Antigens (HLA) or Human Platelet-specific Alloantigens (HPA), and that can result in the generation of antiplatelet antibodies causing refractoriness to donor platelets or post-transfusion purpura, linked to transplant failure after HSCT. Ultimately, this can impact the course of therapy and clinical outcomes.²³⁻²⁵

In this study, the results indicated that for AA patients in the Class 1 trajectory group—specifically those with persistently low platelet levels—platelet transfusion did not improve their 30-day survival rates, suggesting that platelet transfusion may not be an effective strategy for improving survival in this particular patient population. However, this does not imply that platelet transfusion lacks value in all cases. In other patient groups, platelet transfusion may still be necessary to reduce bleeding risk and improve clinical symptoms.²⁶ Therefore, this study recommends that clinicians develop individualized treatment plans for AA patients considering platelet transfusion tailored to the specific circumstances and platelet trajectory of each patient. The findings also

emphasize the importance of considering the dynamic changes in platelet levels in AA treatment and indicate that future research should further explore the benefits of platelet transfusion in different patient populations.

It is clear where we fall short. This study cannot describe the link between AA patients and changes in platelet level trajectories since it is retrospective and has inherent biases. In contrast, prospective studies achieve this goal. More extensive, multicenter prospective trials are therefore required. Secondly, even though selection bias was minimized by PSM analysis, data bias cannot be eliminated due to the extended duration. Third, the absence of markers for hematopoietic function prevented us from determining the severity of AA. Fourth, this study primarily focused on platelet levels, which may not fully capture the complexity of AA patient conditions. Other hematological parameters, such as neutrophil counts, are also important factors in assessing the severity and prognosis of AA. We recommend that future research further explore the role of neutrophil counts and other hematological parameters in the prognosis of AA patients, as well as their interactions with changes in platelet levels. Lastly, our model is based on the MIMIC-IV database, which mostly includes patients from the United States. The study's findings' applicability to the world's population is thus yet uncertain.

Conclusions. Our study identified three different trajectory patterns of platelet levels in AA patients. The increase in platelet levels during hospitalization was associated with improved survival in AA patients. For AA patients who have consistently low platelet levels, platelet transfusion may not be an effective strategy for improving survival rates in this population.

Ethics approval and consent to participate. The dataset is a derivative of MIMIC-IV, and thus, no new patient data was collected. Its ethical approval follows that of the parent MIMIC dataset.

Availability of data and materials. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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