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RESEARCH ARTICLE

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Prognostic value of dynamic cardiac biomarkers in patients with acquired refractory thrombocytopenic purpura: A retrospective study in Chinese population

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Abstract

Introduction: Thrombotic thrombocytopenic purpura (TTP) is becoming a curable disease with the introduction of therapeutic plasma exchange (TPE). However, cardiovascular complications remain essential causes of mortality in patients with refractory TTP, while the association of cardiac biomarkers with the prognosis of TTP warrants further investigation.

Methods: Patients admitted to the First Affiliated Hospital of Soochow University for refractory TTP from 2013 through 2020 were included in this retrospective study. Clinical characteristics were collected from electronic health records. Biomarker levels on admission and post TPE were recorded. Logistic regression was adopted to identify risk factors for mortality.

Results: A total of 78 patients with refractory TTP were included in this study. Twenty-one patients died during hospitalization, with a mortality rate of 26.9%. High-sensitivity cardiac troponin T (hs-cTnT), N-terminal probrain natriuretic peptide (NT-proBNP), and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ratios (AAR) were increased in deceased patients compared with the survival group. Multivariate analysis showed that AAR after TPE was associated with overall mortality (OR: 4.45, 95% CI 1.09–18.19). The areas under the receiver operator characteristic curve (AUC) of AAR, hs-cTnT, and NT-proBNP for the association with mortality were 0.814, 0.840, and 0.829, respectively.

Conclusion: Higher post-TPE cardiac biomarker levels are associated with increased in-hospital mortality in patients with refractory TTP.

KEYWORDS

aspartate transaminase/alanine transaminase ratio, cardiac biomarkers, high-sensitivity cardiac troponin T, N-terminal probrain natriuretic peptide, refractory thrombotic thrombocytopenic purpura

Yinan Xu, Chengyuan Gu and Ruju Wang contributed equally to this study.

1 | INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a severe hematologic emergency with an incidence rate of 3–11 per million people. The mortality rate of TTP reached up to 90% in the pretherapeutic plasma exchange (TPE) era.[1] With the emerging application of TPE in treating TTP, recent years have seen a dramatic improvement in the prognosis of TTP patients. After successful eradication of circulating anti-ADAMTS13 autoantibodies and supplement of functional exogenous ADAMTS13, 78% of the patients with TTP in this era may survive.[2] The current standard of care for TTP includes TPE, corticosteroids, and rituximab. Despite the evolutionary therapies, relapsed and refractory TTP remain a major challenge in clinical practice with a mortality rate exceeding 10%.[3]

Cardiovascular complications of TTP were first reported in a patient whose postmortem autopsy revealed diffusive thrombosis of terminal arteries and capillaries. Subsequently studies demonstrated that acute myocardial infarction and cardiac arrest are the leading causes of death in patients with TTP. Clinical investigations indicated that in-hospital mortality was higher in patients with TTP and major cardiovascular complications (19.7%) than in those without cardiovascular complications (4.1%).[4] Interestingly, clinical manifestations of the cardiovascular system are subtle in most TTP patients.

Reflecting different aspects of cardiac damage, the wide spectrum of biomarkers has facilitated the evaluation and risk stratification of cardiovascular disease beyond clinical manifestation and radiological findings. High-sensitivity cardiac troponin T (hs-cTnT) and N-terminal probrain natriuretic peptide (NT-proBNP) are the most widely used cardiovascular biomarkers in clinical practice. A large-scale cohort study displayed that hs-cTnT is more efficient than conventional troponin in the diagnosis and prognostic evaluation of acute coronary syndromes.[5] NT-proBNP is secreted by cardiomyocytes upon mechanical and hypoxic stresses and is considered a classical biomarker of congestive heart failure.[6] Beyond these conventional biomarkers, novel biomarkers including miRNAs, mimecan, and AST/ALT ratio (AAR) are shedding light on the prognosis of cardiovascular disease.[7] In intensive care unit (ICU) settings, increased AAR is associated with adverse cardiac functional status in patients with heart failure, even after multivariate adjustment for NT-proBNP, hypertension, BMI, age, and diabetes.[8]

2 | METHODS

2.1 | Study population

Patients diagnosed with refractory TTP from 2013 through 2020 at the First Affiliated Hospital of Soochow University were enrolled in this study. The inclusion criteria were: (1) fever, hematuria, neurological involvement, or other TTP manifestations; (2) acute peripheral thrombocytopenia ($<100 \times 10^9$/L) but no other identifiable cause; (3) decreased ADAMTS13 activity level (<10%); (4) positive anti-ADAMTS13 autoantibodies; (5) failure of platelet response after 4–7 days of TPE; (6) a clinical deterioration in a patient receiving standard therapy. Exclusion criteria: (1) age below 18 or above 85 years; (2) pregnancy; (3) hematological or other malignancies; (4) post medical history of congestive heart failure, coronary heart disease, or peripheral arterial disease; (5) pulmonary embolism or deep vein thrombosis; (6) severe renal (eGFR <30 ml/min/1.73 m^2) or hepatic (Child-Pugh class B or C) dysfunction; (7) psychological disease (including history of schizophrenia or depression); (8) recent cerebral vascular disease within 3 months. The study is approved by the ethics committee of the First Affiliated Hospital of Soochow University. All protocols are in accordance with the Declaration of Helsinki.

2.2 | Clinical management

Enrolled patients in this study received standard care despite Caplacizumab, which had not been approved by Sino Food and Drug Administration (SFDA).[9] All patients underwent intensive care, ICU monitoring, enhanced TPE with increased dosage and frequency, rituximab, and steroid therapy. Patients were transferred to an ordinary ward for subsequent treatment after stable amelioration in platelet counts.

2.3 | Data collection

Baseline characteristics, including demographic information, clinical manifestations, and previous medical history, were collected from electronic health records (EHR). Laboratory information, including AST, ALT, hs-cTnT, and NT-proBNP, were collected and recorded on admission and on the next day after last TPE treatment, respectively.

2.4 | Statistical analysis

Continuous data with normal or skewed distributions were present as mean ± standard deviation or median with interquartile ranges and compared between groups using Student's *t*-test or Mann–Whitney nonparametric test. Categorical variables were presented as percentages and compared using Pearson's chi-square test or Fisher's exact test. Multivariate logistic regression was used to analyze the association of variables with mortality events. The concordance of each variable for the risk of death was analyzed using the receiver operating characteristic (ROC) curves and quantified by calculating the area under the ROC curve (AUC). A two-sided p value of <0.05 was considered statistically significant. Data analyses were performed using the IBM SPSS Statistics 26 software.

3 | RESULTS

A total of 78 patients with refractory TTP were included in this study. Twenty-one patients died during hospitalization with a mortality rate

TABLE 1 Demographic and clinical characteristics of survival group and death group of thrombotic thrombocytopenic purpura (TTP)

Clinical characteristics	Survival group ($n = 57$)	Death group ($n = 21$)	p
Age (years)	43.21 ± 14.16	52.38 ± 12.85	**0.028***
Gender			
Male	26 (45.6%)	10 (47.6%)	
Female	31 (54.4%)	11 (52.4%)	0.875
Blood types			
A	14 (24.6%)	8 (38.1%)	0.163
B	18 (31.6%)	5 (23.8%)	
AB	9 (15.8%)	0 (0.0%)	
O	16 (28.1%)	8 (38.1%)	
Symptoms			
Fever	37 (64.9%)	17 (81.0%)	0.173
Petechiae	42 (73.7%)	12 (57.1%)	0.16
Hematuresis	27 (47.4%)	7 (33.3%)	0.268
Conscious disorder	35 (61.4%)	17 (81.0%)	0.104
Immune diseases			
Immune diseases	34 (59.6%)	17 (81.0%)	0.079
Anti-SSA+	23 (44.2%)	7 (50.0%)	0.700

of 26.9% (21/78) and a median time to in-hospital death of 8.05 days. Clinical characteristics were shown in Table 1.

Compared to the survival group, those who died in hospital were older, (52.4 ± 12.9 vs. 43.2 ± 14.2 years, $p = 0.028$), whereas no significant differences were identified in sex, blood group, symptoms, and immune disorders. Moreover, the nonsurvival TTP patients also displayed larger LA diameters and decreased EF values compared to the survived participants.

We showed that on-admission serum hs-cTnT (66.15 [14–410] vs. 29.31 [12.5–90.04] pg/ml, $p = 0.001$), NT-proBNP (1401 [439.5–4490] vs. 1200.6 [235.18–2756] pg/ml, $p < 0.001$), and AAR (1.97 [1.41–2.86] vs. 1.56 [1.07–2.21], $p < 0.001$) were significantly increased in the patients who died in hospital compared to those who survived. However, these markers were comparable at the time of admission despite the mortality events. In addition, echocardiogram displayed lower left ventricular ejection fraction (LVEF) values (0.57 [0.58–0.63] vs. 0.67 [0.6–0.71], $p = 0.025$) and increased left atrial diameter (39 [38–40.75] vs. 36 [32–38] mm, $p = 0.033$) in patients who died compared to the survived subjects (Table 2).

Next, we assessed the association of different variables with overall mortality in TTP patients. Logistic regression showed that age was associated with overall survival (OS) (OR = 1.05, 95% CI 1.009–1.094). Regarding biomarkers, hs-cTnT, rather than ARR and NT-proBNP on admission, was associated with OS (OR = 1.004, 95% CI 1–1.007). Moreover, logistic regression indicated that AAR after

TABLE 2 Laboratory and echocardiography parameters of survival group and death group of thrombotic thrombocytopenic purpura (TTP) on admission

Parameters	Survival group	Death group	p
Laboratory parameters	$n = 57$	$n = 21$	
PLT ($\times 10^9$/L)	10 (8–17.5)	10 (6–11)	0.182
HGB (g/L)	70 (56.5–92)	65 (52.5–72.5)	0.112
T-BIL (μmol/L)	43.9 (24.15–58.3)	61.35 (40.65–86.17)	**0.006***
ALT (U/L)	24.1 (16.2–40.4)	27.3 (17.65–49.9)	0.338
AST (U/L)	35.1 (27.7–64.1)	52.4 (40.85–122)	**0.003***
LDH (U/L)	822.8 (495.9–1270.85)	838.2 (709–2063.5)	0.062
CK (U/L)	103.3 (43.7–233.2)	148.4 (65.7–414.3)	0.157
eGFR (ml/min/1.73 m^2)	94.62 (74.51–118.51)	87.12 (53.1–108.75)	**0.03***
Cardiac biomarkers	$n = 44$	$n = 18$	
hs-cTnT (pg/ml)	29.31 (12.5–90.04)	66.15 (14–410)	0.095
NT-proBNP (pg/ml)	1200.6 (235.18–2756)	1401 (439.5–4490)	0.353
AAR	1.56 (1.07–2.21)	1.97 (1.41–2.86)	0.124
Echocardiographic parameters	$n = 25$	$n = 5$	
LA (mm)	36 (32–38)	39 (38–40.75)	**0.033***
LVEF	0.67 (0.6–0.71)	0.59 (0.58–0.63)	**0.025***

Abbreviations: AAR, AST/ALT ratio; ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; eGFR, estimated glomerular filtration rate; HGB, hemoglobin; hs-cTnT, high-sensitivity cardiac troponin T; LA, left atrial diameter; LDH, lactateic dehydrogenase; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PLT, platelet count; T-BIL, total bilirubin.

The significance use of bold asterisk values in all tables are $p<0.05$.

TABLE 3 Logistic regression analysis of predictors of mortality in patients with thrombotic thrombocytopenic purpura (TTP) on admission and after therapeutic plasma exchange (TPE)

	On admission			After TPE		
Patient characteristics	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age (years)	1.051	1.009–1.094	**0.016***	1.051	1.009–1.094	**0.016***
Course of disease	1.025	0.986–1.066	0.206	1.025	0.986–1.066	0.206
T-BIL (μmol/L)	1.02	1.004–1.037	**0.014***	1.074	1.037–1.112	**<0.001***
ALT (U/L)	1.009	0.994–1.024	0.26	1.004	0.998–1.009	0.206
AST (U/L)	1.012	0.999–1.024	0.061	1.033	1.012–1.054	**0.002***
LDH (U/L)	1.001	1–1.002	**0.015***	1.004	1.002–1.006	**<0.001***
CK (U/L)	1	0.999–1.001	0.467	1.003	1.001–1.006	**0.011***
AAR	1.273	0.884–1.835	0.195	4.548	2.103–9.837	**<0.001***
Myo (ng/ml)	1.002	0.999–1.004	0.12	1.003	0.999–1.007	0.09
Hs-cTnT (pg/ml)	1.004	1–1.007	**0.031***	1.023	1.001–1.046	**0.04***
NT-proBNP (pg/ml)	1	1.000–1.000	0.24	1.001	1–1.001	**0.007***

Abbreviations: AAR, AST/ALT ratio; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; CK, creatine kinase; CK-MB, creatine kinase MB; hs-cTnT, high-sensitivity cardiac troponin T; LDH, lactate dehydrogenase; Myo, myoglobin; NT-proBNP, N-terminal probrain natriuretic peptide; OR, odds ratio; T-BIL, total bilirubin.

The significance use of bold asterisk values in all tables are $p<0.05$.

TABLE 4 Multivariable logistic regression of the predictors of mortality in patients with thrombotic thrombocytopenic purpura (TTP) after therapeutic plasma exchange (TPE)

Characteristics	**OR**	**95% CI**	***p***
Age (years)	1.135	1.020–1.263	**0.020***
PLT ($\times 10^9$/L)	0.982	0.957–1.009	0.190
T-BIL (U/L)	1.085	1.019–1.155	**0.011***
Cr-S (μmol/L)	1.020	0.993–1.048	0.155
AAR	4.449	1.088–18.191	**0.038***

Abbreviations: AAR, AST/ALT ratio; CI, confidence interval; Cr-S, serum creatinine; OR, odds ratio; PLT, platelet count; T-BIL, total bilirubin.

The significance use of bold asterisk values in all tables are $p<0.05$.

TPE was markedly associated with mortality (OR = 4.548, 95% CI 2.103–9.837). In contrast to admission levels, hs-cTnT (OR = 1.023, 95% CI 1.001–1.046) and NT-proBNP (OR = 1.001, 95% CI 1–1.001) after TPE were also associated with OS (Table 3). According to multivariate analysis, elevated AAR after TPE was associated with a four-fold higher risk of mortality after adjustment for age, platelet count, bilirubin, and serum creatinine (Table 4).

To estimate the prognostic value of the cardiovascular biomarkers for overall in-hospital survival, the AUC of AAR, hs-cTnT, and NT-proBNP on admission and after TPE are calculated (Figure 1). Results showed that hs-cTnT after TPE had the highest AUC (AUC = 0.840), followed by NT-proBNP (AUC = 0.829) and AAR after TPE (AUC = 0.814). The best threshold value of AAR according to the Youden index was 1.8, with a sensitivity of 67% and a specificity of 65% (Figure 1). In contrast, the AUC of hs-cTnT (0.632), AAR (0.614), and NT-proBNP (0.588) on admission were all below 0.75.

4 | DISCUSSION

In this study, we found that AAR, hs-cTnT, and NT-proBNP were increased in TTP patients with in-hospital mortality compared to those in survived patients. Multivariate analyses showed that all these biomarkers were independently associated with the risk of death during hospitalization. Among them, AAR had the highest odds for death and may serve as a potential indicator for risk stratification in patients with TTP.

Nowadays, TTP remains an acute hematologic emergency with a specific mortality rate (80%–90%) without efficient TPE intervention. Organ damage, especially of the cardiovascular system, contributes to mortality in patients with TTP.[8] Nearly 25% of the TTP patients may develop cardiovascular complications, reflected by elevated cardiac troponin levels (>0.25 ng/mL). Of note, cardiovascular involvement is an independent prognostic factor for adverse outcomes in TTP patients.[10–12] However, cardiovascular risk stratification in TTP remains in its infancy. Therefore, we investigated the value of cardiovascular biomarkers in TTP patients, analyzing their association with death outcomes. We found that high levels of hs-cTnT, NT-proBNP, and AAR were independently associated with high mortality in TTP patients. Unexpectedly, we demonstrated that post-TPE levels of the biomarkers may exert superior prognostic power than admission biomarker levels. For instance, only hs-cTnT on admission was significantly associated with in-hospital mortality, while all three indices after TPE were associated with the outcome. Among them, AAR, rather than conventional cardiovascular markers, showed the highest odds for death. These results suggested that dynamic tracking of biomarkers after TPE may have conveyed more accuracy for the prediction of death.

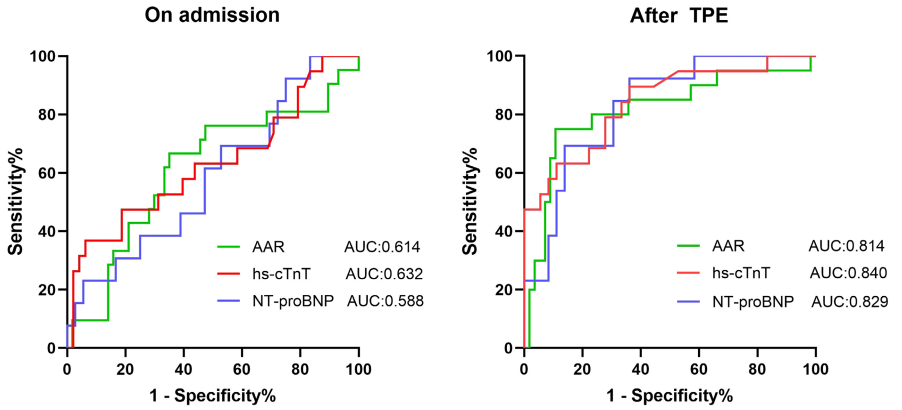

FIGURE 1 Comparison of ROC curves of cardiac biomarkers of mortality in TTP on admission and after TPE

The conventional cardiovascular biomarker hs-cTnT has been established as a gold standard for the detection of myocardial injury, typically in coronary heart disease, congestive heart failure, and cardiac toxicity. The elevation of hs-cTnT due to the release from destroyed cardiomyocytes despite renal dysfunction is considered a highly specific and sensitive cardiovascular biomarker.[13] Its elevation is positively associated with substantial myocardial necrosis caused by an array of different causes, including AMI, pulmonary embolism,[14] sepsis,[15] and community-acquired pneumonia.[16] On the other hand, NT-proBNP is secreted by cardiomyocytes upon mechanical stretch or pressure overload. Moreover, NT-proBNP is released into the bloodstream upon microvascular obstruction.[16,17] Decreased elimination because of aging, renal dysfunction may predispose to higher NT-proBNP concentrations. The kidney is among the most vulnerable organs affected by TTP, and renal dysfunction-related increase in NT-proBNP and hs-cTnT levels may mask their association with death outcomes. Accordingly, we observed only mild association by NT-proBNP and hs-cTnT with in-hospital death before TPE. This is further supported by the restored association of NT-proBNP and hs-cTnT with mortality when renal function was restored after TPE.

AAR was first proposed by De Ritis et al.[18] in 1957 to differentiate viral hepatitis from other types of jaundice-free and frozen liver disease. AST is released from multiple origins, including the liver and myocardium, whereas ALT is secreted exclusively from the liver. To this end, an augmentation of the AAR level is expected upon myocardial injury. Another study showed the prognostic value of AAR in alcoholic hepatitis and cardiac events.[19] In Kawasaki disease, elevated AAR was recognized as a predictor of heart failure and cardiovascular death.[20,21] Mechanistically, high levels of AAR may represent leakage of AST from the injured myocardium.[21] In this study, we found that AAR was a strong risk factor of death in patients with refractory TTP with an optimal cut-off value of 1.8 (sensitivity = 67%, specificity = 65%).[22] Therefore, AAR may be used for TTP risk stratification by reflecting the cardiovascular damage caused by TTP.

In this study, we obtained the post-TPE measurements on the next day after last TPE treatment. The timing may allow us to evaluate the immediate effect of TPE while minimizing the interference by other therapies in a stable condition. Moreover, we excluded those with severe hepatic or renal dysfunction, which may impact the level of serum biomarkers.[23] Patients with history of schizophrenia or depression were also excluded, as the standard therapy for these psychological disorders may also change serum biomarker levels.[24,25] In addition to TPE, the last decade has seen the development of early intervention in specialized ICU, rituximab therapy, N-acetylcysteine, and more recently, Caplacizumab, which lead to great improvements in the prognosis of patients with TTP.[2,26–28] Except for Caplacizumab, which was not approved by SFDA, all subjects in our study received standard care for TTP. As all patients received similar therapeutic intervention, we did not further control for the effect of treatments when analyzing the prognostic role of biomarkers.

Our study has some limitations. First, the outcome measurement for TTP patients was in-hospital mortality and the study was a cross-sectional design. Cohort studies with longer follow-ups in the future will further prove the prognostic value. Second, the study was conducted in the Chinese Han population, thus special caution must be considered while generalizing the conclusion to other populations.

5 | CONCLUSION

In conclusion, our results suggest that increased post-TPE cardiac markers were associated with death in TTP. AAR is a strong predictor for mortality and may be used for risk stratification in future TTP management.

AUTHOR CONTRIBUTIONS

YX, CG, RW, TY, and JF designed the study. YX, CG, RW, JQ, and MJ gathered data. YX, CG, and JF performed the analyses and drafted the first version of the manuscript. JW, TJ, MJ, DW, TY and JF revised the manuscript and approved the last version. All authors revised the manuscript critically for important intellectual content and agree with the final version.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets used to support the findings of the current study are available from the corresponding author on reasonable request.

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