Review Article

A narrative review of clinical biomarkers predicting outcome of immune-mediated thrombotic thrombocytopenic purpura

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Background and Objective: Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) with extremely high mortality rate. Its pathogenesis is severe ADAMTS13 activity deficiency caused by genetic defects or inhibitory antibodies. This leads to ultra-large von Willebrand factor (ULVWF) accumulation, platelet aggregation, microthrombus formation, vital organ damage, and ultimately death. Since most patients are immune-mediated TTP (iTTP) and anti-ADAMTS13 autoantibodies have been recognized as the culprit, treatments including therapeutic plasma exchange (TPE), corticosteroids, rituximab and even caplacizumab are actively adopted. However, further efforts are still needed to reduce mortality and recurrence rates. Doctors are considering whether starting with biomarkers that predict risk may improve treatment decisions. A series of researches emerged coincidentally. This narrative literature review is to summarize and understand these research results.

Methods: MEDLINE online search from 1945 to April 27th, 2023 was set out with strategy of 'thrombotic thrombocytopenic purpura' in MeSH Major Topic and 'biomarkers' in MeSH Terms. Furthermore, hand searches of the references of retrieved literature were applied.

Key Content and Findings: Many researchers provided data involved in ADAMTS13, endothelial injury, acute inflammation, complement activation, cardiac biomarkers, and coagulation parameters. Plasma levels of these biomarkers were detected in iTTP patients and health control. The association of parameters with disease severity, and outcome was analyzed.

Conclusions: Among these biomarkers, ADAMTS13 activity, big endothelin-1 (bigET-1), soluble thrombomodulin (sTM), syndecan-1 (Sdc-1), histone/deoxyribonucleic acid complexes, cell-free DNA (cfDNA), citrullinated histone 3 (CitH3), S100A8/A9, lactate dehydrogenase (LDH) and troponin appear to have evidence in predicting outcome of iTTP patients such as the risk of mortality or refractoriness, which may serve as a useful tool for clinicians and help them to stratify patients and develop better management strategies.

Keywords: Thrombotic thrombocytopenic purpura (TTP); biomarker; outcome

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Introduction

Thrombotic thrombocytopenic purpura (TTP), as a kind of thrombotic microangiopathy (TMA), is characterized by severe thrombocytopenia and microangiopathic hemolytic anemia with various degrees of end organ damage (1,2). Its pathogenesis is severe ADAMTS13 activity deficiency caused by genetic defects or inhibitory antibodies. Naturally, clinical TTP includes congenital TTP (cTTP) and immune-mediated TTP (iTTP) which accounting for 5% and 95% respectively. Although it is a rare disorder, its mortality rate will exceed 90% if the correct treatment is not adopted in time (3,4).

ADAMTS13, as von Willebrand factor (VWF)-

Table 1 The search strategy summary

Items	Specification
Date of search	April 27th, 2023
Databases and other sources searched	MEDLINE online, hand searches of the references of retrieved literature
Search terms used	"thrombotic thrombocytopenic purpura"[MeSH Major Topic]
	"biomarkers"[MeSH Terms]
Timeframe	1945–April 27th, 2023
Inclusion criteria	Language restricted to English and Chinese
Selection process	The author read each abstract to select literature which is really involved in biomarkers of iTTP patients and read the original article if more detail is needed. In addition, the author hand searched and read those useful references of the original article

iTTP, immune-mediated thrombotic thrombocytopenic purpura.

cleaving protease, is a member of the ADAMTS family of metalloprotease, consists of 1,427 amino acid residues and has a signal peptide, a short propeptide terminating in the sequence RQRR, a reprolysin-like metalloprotease domain, a disintegrin-like domain, a thrombospondin-1 repeat, a Cys-rich domain, a spacer domain, seven additional thrombospondin-1 repeats, and two CUB domains (5). When plasma ADAMTS13 activity is inhibited by anti-ADAMTS13 autoantibodies, newly released endothelial ultra-large VWF (ULVWF) and circulating VWF cannot be cleaved in time, ULVWF strings will collect platelets and trigger thrombosis formation in terminal arterioles and capillaries which leads to excessive microvascular thrombosis, end organ damage, and death (6-8).

Therapeutic plasma exchange (TPE), in conjunction with immunosuppressive therapies including corticosteroids and rituximab (9,10) has significantly reduced the mortality rate of iTTP from 90% to ~20% (11). More recently, a nanobody named caplacizumab has been recommended as a novel therapy. It can target the VWF A1 domain, prevent platelet-VWF interaction and hinder thrombus formation. Although this novel therapy might increase iTTP survival (12); the recurrent rate of iTTP patients is still as high as 30% (11). Clinicians hope to identify those patients who are prone to exacerbate and/or relapse, so as to take more timely and better treatment. This article tries to hitherto review the literature on clinical biomarkers which might have predictive values to iTTP patients. This article is presented in accordance with the Narrative Review reporting checklist (available at https://aob.amegroups.org/article/view/10.21037/aob-23-17/rc).

Methods

Information used to write this paper was collected from the sources listed in *Table 1*.

Results

MEDLINE online search from 1945 to Apr 27th, 2023 with 'thrombotic thrombocytopenic purpura' in MeSH Major Topic and 'biomarkers' in MeSH Terms. In total, 162 hits were searched from Medline. With language restrictions of English and Chinese, 142 articles remained. The author read each abstract to select literature which is really involved in biomarkers of iTTP patients and read the original article if more detail is needed. In addition, the author hand searched and read those useful references of the original article. Finally, the synthesis of clinical biomarkers that can predict outcome of iTTP patients is made below.

The role of analysis involved ADAMTS13 such as activity, antigen, and inhibitors or auto-antibodies against ADAMTS13 in risk stratification and prediction of outcomes

ADAMTS13 is primarily synthesized in the interstitial hepatic stellate cells (13). The structure and function of circulating ADAMTS13 has been well investigated (5,14). Among the mature form of ADAMTS13, the proximal MDTCS fragment which include metalloprotease (M), disintegrin-like (D), thrombospondin-1 (T), Cys-rich (C), and spacer (S) domains, has been identified to be enough

for substrate efficient cleavage (15-18), but the S domain of ADAMTS13 is the most important part in discerning and cleaving substrate (18-21). When bound to a surrogate substrate (VWF73), the M, D, C, and S domains experience an important rearrangement, while the TSP1-1 domain acts as a "hinge", laying the S domain near the M domain (16). The CUB domains may associate with the S domain and prevent ADAMTS13 from indiscriminately cleaving VWF for self-regulation (22-24).

Plasma ADAMTS13 activity

The evidence on making earlier and better diagnosis and differentiation is limited and heterogeneous. Clinical criteria or a risk assessment score (either French score or PLASMIC score) is helpful for assessing the pretest probability for iTTP. If French score is higher than 2 or PLASMIC score is higher than 5, ADAMTS13 testing should be obtained (2). Clinical assays for ADAMTS13 activity have an analytical sensitivity of 0.1 to 10 U/dL (or 0.1% to 10%) and seem to be adequate for establishing the initial diagnosis of iTTP (25-27). Almost all iTTP patients have extremely low or undetectable plasma ADAMTS13 activity (<10 U/dL) at the time of diagnosis (28,29). Many patients did not recover their plasma ADAMTS13 activity days and weeks after treatment with TPE, steroids, and/or rituximab. In some patients who have achieved clinical response or remission, plasma ADAMTS13 activity may still be quite low. There is evidence to suggest that plasma ADAMTS13 activity below 10 U/dL after 3 to 7 days' treatment or at the time of initial clinical response, is strongly related to an increased risk of exacerbation or relapse (29-32).

Plasma ADAMTS13 antigen

The plasma ADAMTS13 antigen has not been used for the preliminary diagnosis of iTTP as there is a significant variation in plasma levels of ADAMTS13 during the disease process. Although patient population and timing of sampling may generate inconsistent results, some reports show extremely low ADAMTS13 antigen level in an acute iTTP was significantly associated with higher mortality (33,34) and low plasma ADAMTS13 antigen during remission is associated with a high risk of disease recurrence (29,31).

Inhibitors or anti-ADAMTS13 antibodies

The plasma levels of autoantibodies against ADAMTS13 or inhibitors can be quantified through a mixing study with a functional assay (35,36). But a negative result of functional inhibitor test does not rule out the diagnosis of iTTP. A method for detecting polyclonal anti-ADAMTS13 immunoglobulin G (IgG) based on enzyme-linked immunosorbent assay (ELISA) (37,38), appears to be more sensitive than a functional assay. The role of detecting inhibitors during an acute episode in predicting mortality and disease severity is still controversial. It is demonstrated that higher anti-ADAMTS13 IgG level at presentation may predict higher mortality (34). Although IgG4 is the most common subtype (90%), high level of IgG1 (accounting for 54% subtype) was associated with iTTP mortality (39). In addition, the presence of anti-ADAMTS13 IgA was closely associated with platelet count at presentation and higher anti-ADAMTS13 IgA level may be associated with an increased mortality rate during the acute episode (31,39,40). It was found that high level of anti-ADAMTS13 IgG after 3 to 7 days treatment, but not on admission, was related to increased risk of iTTP exacerbation (29). The presence of ADAMTS13 inhibitors in remission indicated a higher risk for iTTP recurrence (31,40).

The roles of the biomarkers associated with endothelial injury in risk stratification and prediction of outcomes.

VWF antigen and collagen-binding activity (VWF-CBA)

VWF is mainly synthesized in megakaryocytes and vascular endothelial cells. The VWF can interact with many proteins exist in plasma and matrix, such as collagen, platelet glycoprotein 1b, and coagulation factor VIII (41). In plasma, VWF exists in the form of a series of repeated subunits. Under reducing conditions, each VWF subunit contains 2,050 amino acid residues with a molecular weight of approximately 250 kDa. At the sites of vascular injury in vivo, the release of VWF can be triggered (42). VWF secreted from endothelial cells quickly forms "strings or bundle-like" structures under flow (43), thereby enhancing the adhesion function of VWF in normal hemostasis. On the other hand, ADAMTS13 cleaving VWF multimers is vital for maintaining normal hemostasis (44,45).

Clinical observations show that admission levels of plasma VWF-CBA in newly diagnosed or relapsed iTTP were statistically higher than those in healthy controls (28,46-48). In addition, the ratio of VWF-CBA to VWF antigen, was found to be significantly lower in newly diagnosed iTTP patients compared to healthy controls (28). Although the VWF antigen is thought to be a biomarker of organ damage, there has no data about its relationship with

mortality or recurrence rate yet.

Big endothelin-1 (bigET-1)

Endothelin-1 (ET-1) is synthesized and released continuously from endothelial cells. It is a potent vasoconstrictor and can cause inflammation directly (49,50). Besides, it may trigger neutrophil adhesion and mediate VWF expression and release by endothelial cells (50,51). Then induce both neutrophil and platelets driven thrombotic inflammation and organ damage. The plasma half-life of bioactive ET-1 is too short to be used as a diagnostic marker. However, the clearance of its precursor bigET-1 is much slower and has higher plasma stability (49). Furthermore, bigET-1 is produced at an equal molar amount as ET-1, so it is more suitable for diagnostics and monitoring of a disease process (52).

We demonstrated that the plasma level of bigET-1 on admission was significantly increased in acute iTTP patients, and was dramatically decreased when patients achieve response and remission (51). Despite all this, the plasma bigET-1 levels in iTTP patients who had achieved clinical response or remission were still considerably higher than those in health control. This indicated that the recovered iTTP patients had a persisting endothelia dysfunction. Increased plasma bigET-1 levels in iTTP patients on admission were related to the disease severity such as renal insufficiency and intensive care unit (ICU) admission or intubation needed (51). Furthermore, increased admission plasma bigET-1 levels in iTTP patients with an initial episode were associated with poor outcome such as low 60 days survival (51). This is consistent with the other group's results. They found that patients with iTTP had an increase in C-terminal proendothelin-1 (CT-proET-1) in both the acute and remission phase. At the same time, they found that CT-proET-1 level is higher in acute phase compared to the remission phase in the paired sample (53).

Soluble thrombomodulin (sTM)

Thrombomodulin (TM) as a type I transmembrane protein, is one of the main components of the endothelial glycocalyx which is a membrane binding macromolecule on the surface of vascular endothelial lumen (54). It binds to exosomes I on thrombin, altering the specificity of thrombin for protein C (55). Thrombin-TM complex activates protein C and thrombin-activated fibrinolysis inhibitor (TAFI) (56), thereby inhibiting thrombosis (57) and complement activation (58). The ectodomains of TM is cleaved from endothelial cell when being stimulated by tumor necrosis factor-alpha (TNF-α) (59). Plasma or serum levels of sTM are significantly increased in patients with severe diseases such as trauma, organ failure, pulmonary embolism and disseminated intravascular coagulation (DIC) (60). Serum sTM levels seem to be associated with the clinical course of DIC, multiple organ dysfunction syndrome (MODS), and mortality in patients with sepsis (61,62).

It was reported that the levels of plasma TM were not only significantly elevated in iTTP than those in healthy individuals (48,63-65), but also dramatically increased in iTTP patients who suffered from organ failure compared to those who do not have organ failure (66), and related to the severity of iTTP (63,64). Our recent research confirmed these results in a relatively larger iTTP patient's cohort which involved 91 unique iTTP patients with 107 acute episodes (67). Elevated plasma levels of sTM admission are related to the severity of the disease, such as coma, renal failure, needs for ICU or intubation, and hospital mortality (67).

Syndecan-1 (Sdc-1)

Sdc-1, a single pass type I transmembrane proteoglycan, is another component of the endothelial glycocalyx (68). Sdc-1 comprises a core protein and of at least one glycosaminoglycan chain covalently bonded to the protein. The extracellular domain of Sdc-1 will be cleaved under certain pathologic conditions such as acute inflammation (69). It has been observed that patients with inflammation, sepsis, trauma, shock, DIC, and respiratory failure have increased plasma Sdc-1 (70-74).

Different from the biomarker of TM, Sdc-1 was seldom reported in iTTP patients. Given that increased plasma levels of Sdc-1 found in critically ill patients, we pay attention to the relationship between plasma levels of Sdc-1 and outcome of iTTP patients. In our recent iTTP patient's research, we found iTTP patients had increased Sdc-1 in plasma compare to healthy controls (67). Similar to sTM, increased Sdc-1 in patient's plasma is related to disease severity such as coma, needs for ICU or intubation, and mortality in iTTP patients with acute episode (67). When patient's plasma Sdc-1 increased simultaneously with sTM on admission can firmly predict high mortality compared to a single sTM or Sdc-1 increase (67). Furthermore, an additional Sdc-1 and sTM simultaneous increase in plasma during clinical response/remission is associated with recurrence of iTTP patients (67).

The roles of the biomarkers associated with acute inflammation in risk stratification and prediction of outcomes

Human neutrophil peptides (HNP)

Human neutrophil peptides 1–3 (HNP1–3), comprising approximately 5% of total neutrophil protein, are the most plentiful neutrophil granule proteins. They are secreted in response to the activation of neutrophils (75). Apart from being an effective antibacterial agent, HNP1–3 also functions as an immune regulatory molecule, such as inducing cytokine production and activating immune cells (76,77). Furthermore, it is demonstrated that neutrophil defensin could promote clot formation (78) and regulate endothelial stability (79). It was observed that HNP1–3 levels were dramatically increased in patients of acute myocardial infarction when compared to the controls (80). In addition, it was reported that HNP1–3 levels were statistically increased in the active rheumatoid arthritis patients compared to the patients in remission (81).

When take a look in iTTP patients, the plasma levels of HNP1–3 were significantly higher than those of healthy controls (82). Although the levels of HNP1–3 in plasma were significantly elevated in patients with an initial, exacerbated or relapsed episode, it couldn't predict adverse outcome in iTTP patients (28).

Neutrophil extracellular traps (NETs) biomarkers

When infection or inflammation occurs, neutrophils secret chromatin fibers, named as NETs, which help host defense by binding microorganisms (83), while NETs fix platelets and red blood cells to stimulate thrombosis (84,85). NETs are composed of nucleic acid materials, which do not contain any other cytoskeleton proteins. Nucleic acid materials include DNA and granular proteins. DNA is the main component of NETs, forming a skeletal structure that immobilizes various protein particles. The biomarkers of NETs include histone/deoxyribonucleic acid complexes (histone/DNA complexes), cell-free DNA (cfDNA), citrullinated histone 3 (CitH3) and S100A8/A9.

It is reported that acute TMAs are accompanied by high level of plasma DNA or nucleosomes (86). Plasma levels of histone/DNA complexes in acute iTTP patients with an initial, exacerbated or relapsed episode were significantly higher than those in the healthy controls (28,87). Higher Plasma levels of histone/DNA complexes, cfDNA and CitH3 in acute iTTP patients on admission were associated with low survival rates (87). Patients of iTTP with small ischemic stroke on neuroimaging had higher plasma levels of histone/DNA complex than those with large strokes. However, there were no significant differences between 2 stroke groups in mortality or exacerbation (88). Recently, it was demonstrated that histone-induced TTP in adamts13$^{-/-}$ zebrafish depends on VWF which indicated inflammation might be a probable mechanism of TTP characterized by severe A13 deficiency (89).

S100A8/A9 are heterodimers mainly released from activated or necrotic neutrophils and monocytes/macrophages (90,91). As a marker for NETs releasing and neutrophil activating (92), S100A8/A9 can be used as a diagnostic marker of noninfectious inflammatory diseases such as intestinal diseases, chronic inflammatory pulmonary and arthritis (93,94). More recently, it is demonstrated that S100A8/A9 may play a role in thrombosis (95-97). It is also reported that the level of plasma S100A8/A9 is associated with the mortality of ischemic stroke (98). Earlier research and our recent study showed the level of plasma S100A8/A9 was statistically increased in iTTP patients of initial episode and normalized in clinical remission (86,87). The elevated plasma S100A8/A9 is also correlated with myocardial ischemia and survival in these iTTP patients (87).

Lactate dehydrogenase (LDH)

LDH is a very common enzyme in nature. It exists in the cytoplasm and is released into the plasma after cell damage. Since the increase of plasma LDH level reflects the degree of tissue damage, it has been used as a risk factor in patients with many diseases, including severe infections, cancer, cardiac disease and liver disease. During NET formation, LDH is released from dying neutrophils (99). Significant increase in plasma LDH levels in patients with acute TMAs (86). iTTP as a typical TMA, plasma levels of LDH were strongly elevated in iTTP patients of initial episode (28,82,100-102). High level of LDH on admission in refractory iTTP patients may indicate mortality (103). It is reported the decline LDH ratio of acute iTTP patients from the first to the third cycle of plasma exchange can predict the individual response (104). Similarly, another report shows substantial reduction of LDH in 5 days of plasma exchange is associated with good survival (28).

The roles of complement activation biomarkers in risk stratification and prediction of outcomes

The complement system is a component of the innate immune response and serves as a link between innate

and acquired immunity. The main function of the complement system is to protect the host from infection or inflammation by recruiting and enhancing the phagocytosis of innate immune cells, thus leading to the dissociation of target cells (105,106). Complement dysregulation is an important pathogenesis of atypical haemolytic uraemic syndrome (aHUS) (107,108). More recently, complement dysregulation is also reported in acute iTTP patients. Staley *et al.* reported that acute iTTP patients' plasma levels of Bb, iC3b and sC5b-9 were significantly elevated when compared to healthy controls (28). Réti *et al.* showed that plasma levels of C3a, and SC5b9 in acute iTTP patients were higher than those in healthy controls (109). Westwood *et al.* and Wu *et al.* agree that median C3a and C5a were statistically increased in iTTP during initial episode, when compared to remission (110,111). Staley *et al.* failed to demonstrate a significant difference in Bb, iC3b and sC5b levels between the alive group and the death group (28). However, Wu *et al.* reported higher plasma levels of Bb, C3a, C5a, and C5b-9 in dying patients of acute iTTP episode compared to those responding to treatment (111). It may indicate that the dead patients could suffered from both severe ADAMTS13 deficiency and dysregulation of complement activity. Higher levels of SC5b-9, C3a and C5a facilitate the formation of ULVWF multimers, indicating a link between complement activation and ULVWF multimers (112).

The roles of cardiac biomarkers in risk stratification and prediction of outcomes

Degree of organ ischemia and involvement caused by microthrombus are changeable in iTTP patients. Different from aHUS, renal injury is uncommon in iTTP. More than 60% of patients have neurological manifestations (4,11,113-115), gastrointestinal ischemia is present in 35% of patients (4). One-quarter of acute iTTP patients have evidence of myocardial ischemia, presented with abnormal electrocardiogram or increased plasma troponin levels (116). About 95% of patients tested in the emergency department (ED) have serum troponin levels higher than normal, and approximately 87% of patients tested after admission still have troponin levels higher than normal (28). High troponin levels on at ED were significantly associated with in-patient mortality (28).

In a study including 78 patients with refractory iTTP, on-admission serum high-sensitivity cardiac troponin T (hs-cTnT) was significantly increased in the patients who died in hospital compared to those who survived. Logistic regression showed that hs-cTnT was associated with overall survival (103). From a cohort of 41 patients, two-thirds of the cases had elevated levels of troponin T upon admission. Patients with elevated ADAMTS13 IgG antibody levels had higher troponin T levels (>0.1 μg/L), which are associated with higher morbidity and acute mortality (117).

In one study of 68 iTTP patients admitted 88 times, although non-survivor iTTP patients had significantly higher creatine kinase (CK), CK-MB, and troponin I at the first measurement, only troponin I remained significant on multivariate analyses (102). In another study of 133 patients with iTTP, 59% patients had increased troponin I level (>0.1 μg/L) on admission. Elevated troponin I levels at onset in iTTP patients seem to be an independent factor associated with increased mortality or risk of refractory disease (116).

The roles of coagulation parameters in risk stratification and prediction of outcomes

The levels of prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen, and antithrombin in patients with iTTP remain within normal ranges, while levels of fibrinogen/fibrinogen degradation products (FDP) and D-dimer slightly increase (118).

Recently, Staley *et al.* reported prolonged aPTT and increased fibrinogen in 5 days of plasma exchange is associated with poor survival (28). This report and another study had shown D-dimer level elevated in the iTTP patients with poor prognosis, but without statistical significance (28,119). But there is a single-center observational cohort study which included a total of 87 iTTP admissions shows that patients with a high D-dimer level at admission could fall into poor outcome and require more intensive treatment (120).

An earlier study found that the plasma tissue-type plasminogen activator (tPA) level was increased and correlated with the outcome in iTTP patients (119). One study including 29 iTTP patients also found most patients have moderate to high plasma levels of total plasminogen activator inhibitor-I (PAI-I) and tPA/PAI-I complex (66). Another study found PAI-I and tPA/PAI-I complex were strongly elevated in 39 TTP/HUS patients; but the levels of PAI-I and tPA/PAI-I complex were not statistically different between survived and dead TTP/HUS patients (64).

Discussion

Through reading the retrieved literature, it was found

that the biomarkers involved in iTTP include aspects of ADAMTS13, endothelial injury, acute inflammation, complement activation, cardiac biomarkers, and coagulation parameters. The author has tried to search literature through specific terms such as D-dimer, VWF, endothelin, Sdc-1, etc., but those searched issues were not beyond the results of biomarkers when combined to TTP. In order to provide readers with a more convenient and clear understanding of the role of these biomarkers in iTTP prognosis, the author has compiled a table, as shown in *Table 2*.

Among the analysis involved ADAMTS13, it is plasma ADAMTS13 activity but not antigen has determinative importance for diagnosis of iTTP. High risk of exacerbation or relapse seems related to persisting low plasma ADAMTS13 activity, extremely low plasma ADAMTS13 antigen and persisting existence of anti-ADAMTS13 antibody during treatment and clinical response. While extremely low plasma ADAMTS13 antigen and high level of anti-ADAMTS13 antibody on admission is associated with increased mortality.

As biomarkers associated with endothelial injury, plasma VWF antigen and VWF-CBA were found to have no predictive value in iTTP. However, plasma bigET-1, sTM and Sdc-1 were shown relationship with iTTP severity and poor survival. More specifically, high plasma bigET-1 and sTM levels could both presage renal failure, while high sTM and Sdc-1 levels are both related to disturbance of consciousness. Furthermore, the simultaneous increase in plasma sTM and Sdc-1 levels is more valuable in predicting mortality or recurrence compared to a single increase in sTM or Sdc-1.

Regarding inflammatory biomarkers, there is no evidence of prediction value of plasma HNP1–3 in iTTP patients. Conversely, elevated admission plasma level of NETs biomarkers such as histone/DNA complexes, cfDNA, CitH3 and S100A8/A9 may all indicate poor iTTP survival. Even LDH level on admission in refractory patients and LDH decrease extent after plasma exchanges may predict mortality in iTTP patients.

The value of complement factors in aspect of prognosis prediction is controversial. However, high troponin levels on admission were significantly associated with mortality both troponin I of initial episode and high-sensitivity

Table 2 Summary of biomarkers and their roles in outcome of iTTP

Biomarkers	Role in predicting outcome of iTTP patients	References
Biomarkers involved ADAMTS13		
Plasma ADAMTS13 activity	Clinical assays for ADAMTS13 activity have an analytical sensitivity of 0.1 to 10 U/dL (or 0.1% to 10%) and seem to be adequate for establishing the initial diagnosis of iTTP	(25-27)
	Plasma ADAMTS13 activity below 10 U/dL after 3 to 7 days' treatment or at the time of initial clinical response, is strongly related to an increased risk of exacerbation or relapse	(29-32)
Plasma ADAMTS13 antigen	Extremely low ADAMTS13 antigen level in an acute iTTP was significantly associated with higher mortality	(33,34)
	Low plasma ADAMTS13 antigen during remission is associated with a high risk of disease recurrence	(29,31)
Plasma anti-ADAMTS13 IgG	Higher level of anti-ADAMTS13 IgG at presentation may predict higher mortality	(34)
	High level of anti-ADAMTS13 IgG after 3 to 7 days treatment, but not on admission, were related to increased risk of iTTP exacerbation	(29)
Plasma anti-ADAMTS13 subtype	High level of anti-ADAMTS13 IgG1 was associated with iTTP mortality	(39)
	Higher plasma anti-ADAMTS13 IgA level may be associated with an increased mortality rate during the acute episode	(31,39,40)
ADAMTS13 inhibitors	The presence of ADAMTS13 inhibitors in remission indicated a higher risk for iTTP recurrence	(31,40)

Table 2 (*continued*)

Table 2 (*continued*)

Biomarkers	Role in predicting outcome of iTTP patients	References
Biomarkers associated with endothelial injury		
Plasma VWF antigen	There is no data about plasma VWF antigen relationship with mortality or recurrence rate yet	(28,46-48)
BigET-1	Increased plasma bigET-1 levels in iTTP patients on admission were related to the disease severity and low 60 days survival	(51)
sTM	Elevated plasma levels of sTM admission are related to the severity of the disease and hospital mortality	(63,64,66,67)
Sdc-1	Elevated plasma levels of Sdc-1 admission are related to the severity of the disease and hospital mortality	(67)
sTM & Sdc-1	Plasma Sdc-1 increased simultaneously with sTM on admission can firmly predict high mortality compared to a single sTM or Sdc-1 increase, an additional Sdc-1 and sTM simultaneous increase in plasma during clinical response/remission is associated with recurrence of iTTP patients	(67)
Biomarkers associated with acute inflammation		
HNP1–3	HNP1–3 levels couldn't predict adverse outcome in iTTP patients	(28)
Histone/DNA complexes, cfDNA and CitH3	Higher plasma levels of histone/DNA complexes, cfDNA and CitH3 in acute iTTP patients on admission were associated with low survival rates	(87)
S100A8/A9	The elevated plasma S100A8/A9 are correlated with myocardial ischemia and survival in iTTP patients	(86,87)
LDH	High level of LDH on admission in refractory iTTP patients may indicate mortality. Substantial reduction of LDH in 5 days of plasma exchange is associated with good survival	(28,103,104)
Complement activation biomarkers		
Bb, iC3b, C3a, C5a, and C5b-9	Although there is no significant difference in Bb, iC3b and sC5b levels between the alive group and the death group, it is reported higher plasma levels of Bb, C3a, C5a, and C5b-9 in dying patients of acute iTTP episode compared to those responding to treatment	(28,111)
Cardiac biomarkers		
High-sensitivity cardiac troponin T	Serum high-sensitivity cardiac troponin T on-admission was associated with overall survival	(28,103,117)
Troponin I	Elevated troponin I levels at onset in iTTP patients seem to be an independent factor associated with increased mortality or risk of refractory disease	(102,116)
CK, CK-MB	No significant on multivariate analyses	(102)
Coagulation parameters		
aPTT and fibrinogen	Prolonged aPTT and increased fibrinogen in 5 days of plasma exchange is associated with poor survival	(28)
D-dimer	A high D-dimer level at admission could lead to poor outcome and require more intensive treatment	(120)
Plasma tPA	Plasma tPA level was increased and correlated with the outcome in iTTP patients	(119)
PAI-I and tPA/PAI-I complex	The levels of PAI-I and tPA/PAI-I complex were not statistically different between survived and dead TTP/HUS patients	(64)

iTTP, immune-mediated thrombotic thrombocytopenic purpura; IgG, immunoglobulin G; VWF, von Willebrand factor; bigET-1, big endothelin-1; sTM, soluble thrombomodulin; Sdc-1, syndecan-1; HNP1–3, human neutrophil peptides1-3; cfDNA, cell-free DNA; CitH3, citrullinated histone 3; LDH, lactate dehydrogenase; aPTT, activated partial thromboplastin time; tPA, tissue-type plasminogen activator; PAI-I, plasminogen activator inhibitor-I; TTP, thrombotic thrombocytopenic purpura; HUS, haemolytic uraemic syndrome.

troponin T of refractory iTTP. Inconsistent results about coagulation parameters in iTTP patients need more research data.

Due to iTTP being a rare disease, there are few medical centers that can summarize, analyze and publish valuable data about iTTP patients. Not only that, the number of cases analyzed in the published articles is only a few dozen, and many literature reports are combined with other TMAs. Many data of iTTP are sporadic and some studies are still controversial. Therefore, this review may have certain limitations. The conclusions obtained require further research to confirm.

Conclusions

Although much has been learned about clinical and laboratory parameters that might indicate the outcome of iTTP patients. Many biomarkers predict value are not confirmed. But some biomarkers such as ADAMTS13 activity, bigET-1, sTM, Sdc-1, histone/DNA complexes, cfDNA, CitH3, S100A8/A9, LDH and troponin, have convincing prognostic guidance value. This article indicates some biomarkers may help clinicians stratify patients to develop more intensive management strategies, including admission to ICU, early use of caplacizumab, and carefully monitor of vital signs. This may reduce the inpatient mortality rate and subsequent recurrence of iTTP. However, due to the limitations of this article, their clinical value still needs to be confirmed by accumulating more data in the future.

Finally, most of these biomarkers' analyses are limited to laboratories and not widely conducted. For many hospitals, even ADAMTS13 activity testing cannot be done at any time. In the real world, clinical analysis of LDH and troponin is feasible and universal. But at least, clinicians can initially use these available tests to monitor the severity of the disease.

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