

**RESEARCH LETTER**

# Managing surgical relapse risk in acquired thrombotic thrombocytopenic purpura: a systematic review

**Essentials**

- Thrombotic thrombocytopenic purpura (TTP) may relapse after surgery.
- In a systematic review, we assessed preoperative TTP prophylaxis.
- Pre-emptive ADAMTS-13 activity measurement prior to surgery may improve relapse risk.
- Preoperative TTP prophylaxis may lower surgical relapse risk.

Acquired thrombotic thrombocytopenic purpura (TTP) can be triggered by factors such as infections, pregnancy, and surgery [1–3]. Surgery may trigger TTP through direct endothelial injury, indirect endothelial damage, and increased cytokine release. Surgery may also tilt the balance between a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13 (ADAMTS-13) activity and ultralarge von Willebrand factor (ULVWF) [4–8]. In 50% of patients in remission, surgery may also contribute to TTP relapse [3].

In patients with a history of TTP, it is not known how surgery contributes to relapse risk. It is also not known how relapse risk should be managed. While reviewing full text studies for a systematic review of TTP diagnosis following surgical and nonsurgical procedures, we identified a subset of patients with known TTP who underwent surgery [9]. From this subset, we developed a new systematic review to answer the following question: in patients with a history of TTP undergoing surgery, what strategies are used to prevent relapse? These results are presented herein.

From inception to September 11, 2023, a comprehensive search of the literature was conducted using PubMed, Embase, and Scopus (see full search strategy in the [Supplementary Methods](#)). Additional references were identified by hand-searching bibliographies of final included articles. All identified studies were screened in Covidence systematic review software (Veritas Health Innovation) [10]. Two independent reviewers (A.S.F.J. and M.P.M.L.) screened all studies. Any conflicts were resolved by discussion or a binding vote from a third independent reviewer (O.A.O.). Inclusion criteria were 1) patients undergoing surgery with 2) a prior diagnosis of TTP. The TTP diagnosis was defined based on ADAMTS-13 activity of <10% and the presence of anti-ADAMTS-13 antibodies or resolution of ADAMTS-13

deficiency after treatment. Studies were excluded if the study population was exclusively pregnant patients (whose relapse may have been triggered by pregnancy), patients with solid or hematopoietic stem cell transplant, or patients with other types of thrombotic microangiopathy (such as hemolytic uremic syndrome or complement mediated). We also excluded studies reporting patients undergoing surgery as part of their TTP treatment (such as splenectomy or cancer surgery) or patients undergoing surgery during or immediately following the acute TTP episode. Finally, we excluded non-English articles and systematic reviews.

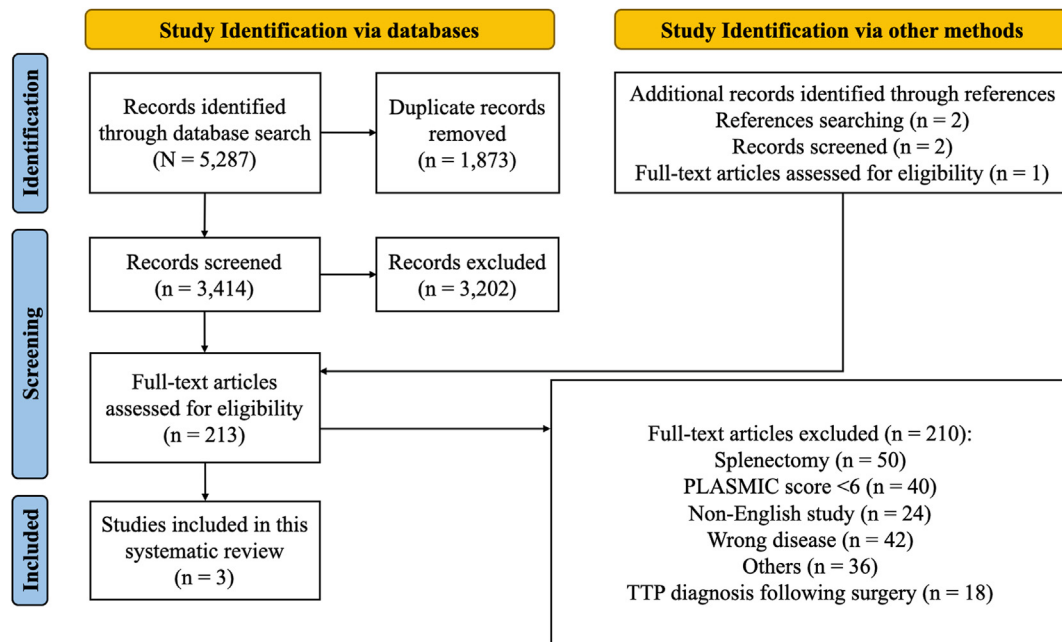
Our systematic review identified 2 case reports and 1 case series (see [Figure 1](#)). These studies included 9 surgeries in 8 patients with a confirmed prior diagnosis of TTP (severe ADAMTS-13 deficiency with inhibitor) [3,11,12]. The average age was 48 years (range, 15–68). Five patients were female (62%) and 3 were male (38%) [3,11,12].

Prior to surgery, the average number of TTP episodes was 4 (range, 1–7). The average time since the last TTP episode was 18 months (range, 1–48) [3,11,12]. One patient (13%) underwent two surgeries: cholecystectomy and total hip arthroplasty. Four patients (50%) underwent abdominal surgery (hernioplasty, hysterectomy, oophorectomy, and liver transplantation) [3,12], and 1 patient each (13%) cardiothoracic surgery (coronary artery bypass grafting), orthopedic surgery (total hip arthroplasty) and head and neck surgery (parotidectomy) [3,11].

At the time of surgery, all patients were in clinical remission (see [Supplementary Table](#)). Prior to surgery, ADAMTS-13 activity was assessed in 7 of 8 patients (87%) [3,12]. Among these 7 patients, severe ADAMTS-13 deficiency (<10%) was reported in 6 [3]. In 1 patient, the ADAMTS-13 activity was about 40% following initiation of

Morgana Pinheiro Maux Lessa and Alexandre Soares Ferreira Junior contributed equally to the development of this project.

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**FIGURE 1** PRISMA flow diagram. There were 5287 references imported for screening and 1873 duplicates removed. The number of studies screened against title and abstract was 3414. Based on the title and abstract screening, 3202 studies were excluded. Additionally, manual reference searching identified 2 studies. Among those, 1 study was assessed for eligibility in full text review. Of all full text studies assessed ( $n = 213$ ), 210 were excluded, including 50 reporting splenectomy, 40 with PLASMIC score  $<6$ , 24 non-English studies, 42 with diseases other than TTP, 36 for other reasons, and 18 with patients with a new TTP diagnosis following surgery. Therefore, the final number of included studies was 3. INR, International Normalized Ratio; MCV, mean corpuscular volume; PLASMIC, platelet count  $<30 \times 10^9/L$ , lysis markers present, active cancer treated within the past year, history of solid-organ or stem-cell transplant,  $MCV <9.0 \times 10^{-14} L$  ( $<90$  fL),  $INR <1.5$ , creatinine  $<2.0$  mg/dL; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses; TTP, thrombotic thrombocytopenic purpura.

TTP-specific therapy (weekly rituximab and every other day therapeutic plasma exchange [TPE]) [12].

To decrease relapse risk in patients with severe ADAMTS-13 activity, the following prophylactic strategies were used: 1) TPE alone ( $n = 5$ ); 2) TPE + rituximab ( $n = 1$ ); 3) TPE + rituximab + plasma infusion ( $n = 1$ ), and 4) azathioprine ( $n = 1$ ; see Figure 2A) [3,12]. Following these prophylactic strategies, repeat ADAMTS-13 activity ranged from 25% to 50%. These 7 patients underwent surgery without relapse (see Figure 2B).

In the 1 patient in whom prophylaxis was not done, TTP relapsed following coronary artery bypass grafting. In this patient, preoperative ADAMTS-13 activity was not assessed and no prophylactic measures were performed [11]. Retrospective ADAMTS-13 activity assessment from preoperative plasma samples showed severe ADAMTS-13 deficiency with inhibitor (see Supplementary Table) [11].

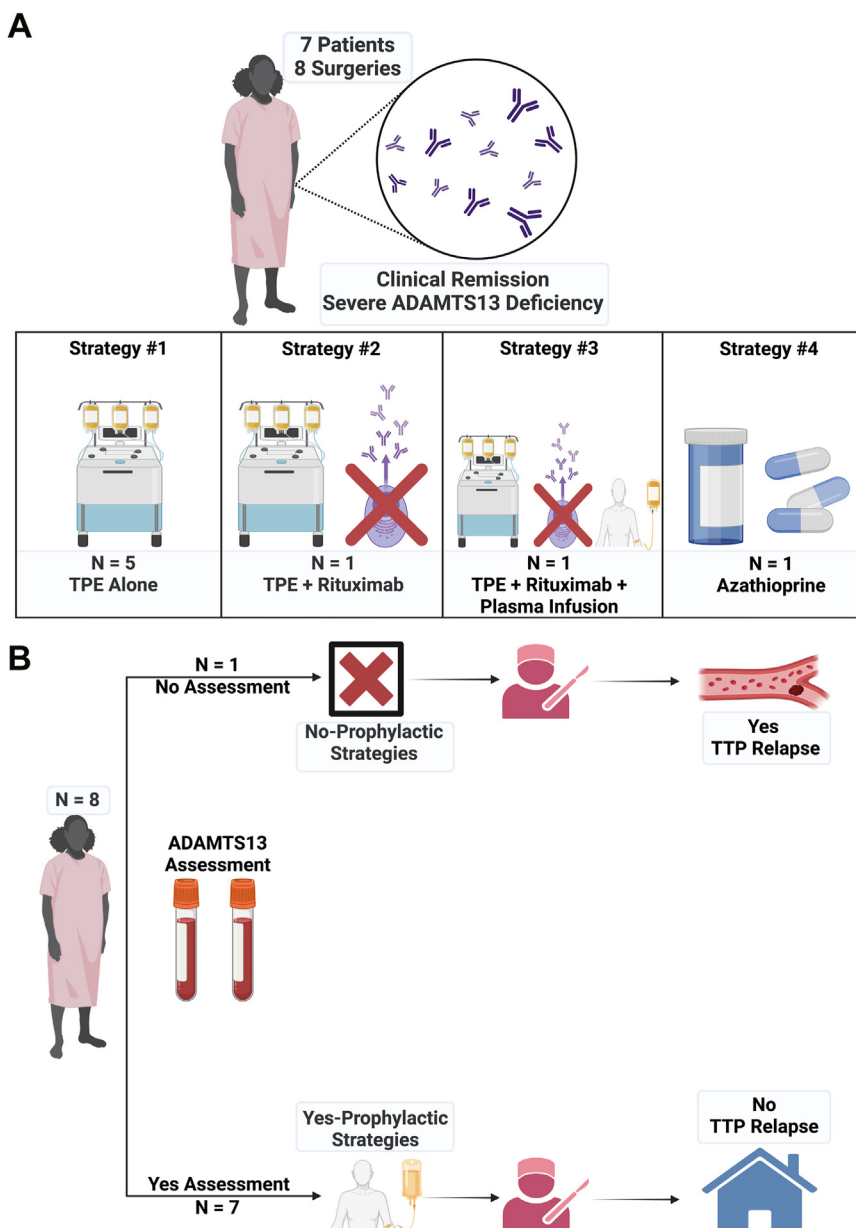
These data may suggest a potential role for ADAMTS-13 assessment prior to surgery in patients with a history of TTP. In patients with known TTP who are undergoing surgery, preoperative assessment of ADAMTS-13 activity levels could guide prophylactic strategies to mitigate relapse risk [3,11,12]. In patients identified to have severe ADAMTS-13 deficiency prior to surgery, prophylactic

strategies may help decrease TTP relapse risk [3,11,12]. As suggested by our findings, prophylactic strategies to decrease relapse risk may enable patients with TTP to safely undergo surgery, even if they do not normalize their ADAMTS-13 activity levels [3,11,12].

An important limitation of this study is that the numbers are small. Additionally, the treatment approaches described are heterogeneous and somewhat outdated (eg, there is little utility for plasma infusion in a patient with inhibitor). Also, the predominance of patients with severe ADAMTS-13 deficiency who remained TTP-free following surgery (6/7) indicates the possibility of publication bias. It is probable that patients with TTP routinely undergo surgeries without any ADAMTS-13 monitoring or treatment.

It is also important to note that almost all patients in this study (6/8) had persistent ADAMTS-13 deficiency at baseline. Therefore, they were not in biochemical remission. Additionally, in the patient who relapsed, ADAMTS-13 activity levels were not checked preoperatively. Therefore, it is uncertain how these study findings might apply in patients with full biochemical and clinical remission. Additionally, due to the small numbers of patients lacking biochemical remission, our study findings cannot be used to make management recommendations for this specific population.

**FIGURE 2** Surgery in patients with TTP in clinical remission. Panel A shows the prophylactic strategies used prior to the surgery. Panel B shows patient outcomes. ADAMTS-13, a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13; TTP, thrombotic thrombocytopenic purpura. Created with [BioRender.com](https://www.biorender.com) accessed on October 26, 2023.



Notwithstanding these limitations, this systematic review suggests the need for planning and pre-emptive ADAMTS-13 activity measurements prior to surgery in patients with TTP.

#### AUTHOR CONTRIBUTIONS

O.A.O. conceived and designed the systematic review. O.A.O., M.P.M.L., and A.S.F.J. developed the systematic review protocol with input from L.L., E.S., and M.G. L.L., E.S., and M.G. performed the literature search. M.P.M.L. and A.S.F.J. created the title and abstract screen, performed full text review, and finalized the list of studies for inclusion. M.P.M.L. and A.S.F.J. performed the data abstraction. O.A.O., M.P.M.L., and A.S.F.J. led the data interpretation. M.P.M.L. and A.S.F.J.






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#### RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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Morgana Pinheiro Maux Lessa<sup>1</sup>    
 Alexandre Soares Ferreira Junior<sup>1,2</sup>    
 Margaret Graton<sup>3</sup>  
 Erin Simon<sup>3</sup>  
 Leila Ledbetter<sup>3</sup>  
 Oluwatoyosi A. Onwuemene<sup>4</sup> 

<sup>1</sup>Department of Medicine, Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto, São Paulo, Brazil

<sup>2</sup>General and Applied Biology Program, Institute of Biosciences (IBB), Sao Paulo State University (UNESP), Botucatu, Brazil

<sup>3</sup>Duke University Medical Center Library, Durham, North Carolina, USA

<sup>4</sup>Division of Hematology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA

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#### Correspondence



Oluwatoyosi A. Onwuemene, Division of Hematology, Department of Medicine, Duke University School of Medicine, 40 Duke Medicine Circle, DUMC Box 3422, Durham, NC 27710, USA.  
 Email: [toyosi.onwuemene@duke.edu](mailto:toyosi.onwuemene@duke.edu)

#### ORCID

Alexandre Soares Ferreira Junior  <https://orcid.org/0000-0002-1256-1249>

Oluwatoyosi A. Onwuemene  <https://orcid.org/0000-0001-7266-7101>

#### X

Morgana Pinheiro Maux Lessa  @morganapinhoiro  
 Alexandre Soares Ferreira Junior  @alexhemostasis

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#### SUPPLEMENTARY MATERIAL

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