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Incidence and Risk Factors of Transplantation-Associated Thrombotic Microangiopathy: A Systematic Review and Meta-Analysis

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A B S T R A C T

Transplantation-associated thrombotic microangiopathy (TA-TMA) is an increasingly recognized post-transplantation complication, yet the overall incidence of the disease remains under debate. To determine the pooled incidence of TA-TMA in a systematic review of literature and to identify consistent risk factors. We performed a systematic review using the MEDLINE, Embase, and CENTRAL databases to identify cohort studies that reported incidence of and risk factors for TA-TMA from 2004 to 2020. We conducted a meta-analysis of proportion to estimate the pooled incidence of TA-TMA using a random-effects model. We assessed moderators of heterogeneity through subgroup analysis, risk of bias through ROBINS-I, and publication bias through funnel plot. Among 21 cohort studies with a total of 36,163 adult and pediatric patients who underwent allogeneic transplantation, the pooled incidence of TA-TMA was 12% (95% confidence interval, 9% to 16%). The diagnostic criteria used to define the disease was the most significant contributor identified to the high interstudy heterogeneity (I^2 = 98%). Studies using provider/clinician diagnosis instead of laboratory diagnosis reported the lowest incidence, at 3%. The most salient risk factor for TA-TMA reported in 14 studies was preceding acute graft-versus-host disease (GVHD). Other risk predictors described in 5 or more studies included preceding infection, prior transplantation, mismatched donor, and myeloablative conditioning. With a pooled incidence at 12% among a significantly heterogeneous population, TA-TMA is an important but relatively uncommon post-transplantation complication. Given the divergence between reported laboratory-based and provider-based incidence, as well as the multitude of risk factors beyond acute GVHD, future studies should focus on risk-stratifying the subset of TA-TMA patients who would benefit from therapeutic intervention.

INTRODUCTION

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a rare but well-recognized potential complication of hematopoietic cell transplantation (HCT). TA-TMA is part of the family of thrombotic microangiopathies, which includes hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and secondary thrombotic microangiopathies. The pathogenesis of TA-TMA involves a complex cascade of events triggered by microvascular endothelial activation from tissue damage brought about by HCT [1]. The release of cytokines from this tissue damage results in further injury to endothelial tissue, ultimately leading to the widespread activation and coagulation of platelets and coagulation factors [2]. This hemolytic process causes the development of microangiopathic hemolytic anemia, thrombocytopenia, and microthrombi in small blood vessels. Together, these hallmarks of TA-TMA induce ischemic tissue injury that can be severe enough to cause significant kidney injury and death [3].

The diagnosis of TA-TMA has evolved with our understanding of the pathophysiology of the disease over the years. Since 2005, the Bone Marrow Transplant Clinical Trials Network (BMT-CTN) and International Working Group (IWG) have published their respective guidance on TA-TMA [4,5]. However, the sensitivity and specificity of these criteria have been called into question, and newer consensus criteria emerged in 2010 that were further modified in 2014 [6,7]. The diverse clinical

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criteria used highlight the diagnostic dilemma and impact the true incidence of the disease.

Although our understanding of the pathogenesis and methods for diagnosis of TA-TMA have been evolving rapidly with recent research, the epidemiology of the condition, including its incidence in adults and children and risk factors for disease development, remains under debate. George et al. [8] analyzed some of these characteristics in a systematic review describing patients with TA-TMA published prior to 2004; however, evaluation of these metrics in more recent studies is warranted, given advances in the understanding of disease pathophysiology, diagnosis, and treatment. To this end, here we report the results of a systematic review and meta-analysis of observational studies examining the incidence of and risk factors for TA-TMA published between 2004 and 2020.

METHODS

Search Strategy and Syntax

Using EMBASE (Elsevier), MEDLINE (Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL) from all languages, we systematically searched the literature for studies related to TA-TMA published between January 1, 2004, and June 14, 2020. The full search strategy used to identify articles is documented in Supplementary Table S1. We also reviewed the references of included studies and narrative reviews to identify additional studies. The protocol for the systematic review and the search strategy were registered online prior to the start of study screening and data extraction (PROSPERO: CRD42020190728) [9]. We used Covidence software (Melbourne, Australia) for deduplication and management of citations [10] and followed the PRISMA guideline for reporting outcomes (Supplementary Table S2) [11].

Study Selection, Data Extraction, and Quality Assessment

Two authors (V.V.B. and R.G.) independently screened all studies returned by the search strategy by examining the titles and abstracts for eligibility. The articles included for further review were cohort studies reporting either the incidence or risk factors for TA-TMA and including 20 or more TA-TMA patients. Articles were excluded if they reported primarily on biomarkers, did not report on incidence or risk factors, or did not have a cohort study design. Article records were independently reviewed for inclusion in duplicate. Discrepancies in study inclusion/exclusion were resolved by a separate reviewer (A.L.).

Following screening and selection of appropriate studies, 2 authors (V.V.B. and C.R.) independently extracted data from the full texts of the studies. Data gathered included number of patients, age, sex, race, type of transplant received, indication for HCT, conditioning intensity, graft-versus-host disease (GVHD) prophylaxis regimen, frequency and grade of acute GVHD, follow-up duration, and overall mortality. TA-TMA-specific information obtained include the diagnostic criteria used, number of reported cases, time to disease onset, risk factors reported in multivariable analysis, treatments used, and disease-specific mortality. Data from each study were extracted using a uniform data extraction form. TA-TMA incidence was defined as a proportion of cases over the HCT recipients during the study-specific follow-up.

A modified version of the ROBINS-I tool from the Cochrane Methods group was used to assess the qualities of the observational studies included in the review [12]. Specifically, we focused on 5 relevant domains: bias in selection, bias because of missing data, bias in measurement of outcomes, bias in selection of reported results, and confounding. Publication bias was assessed using funnel plots of study effect size plotted against study sample size.

Statistical Analysis

Among selected cohort studies that reported the incidence of TA-TMA, a meta-analysis of proportion was performed using the *metaprop* package of Stata 16.1 (StataCorp, College Station, TX) [13]. Specifically, the confidence intervals (CIs) for each study were estimated using the Clopper-Pearson exact binomial method [14]. The pooled estimate was stabilized with the Freeman-Tukey double arcsine transformation [15] and compared using the DerSimonian-Laird random-effects model [16]. Forest plots were used to show the pooled proportion and 95% CIs across the studies. Additional prespecified subgroup analyses were performed based on diagnostic criteria used, study size, median age of participants, and prevalence of malignancy among participants. Between-study heterogeneity was assessed using the I^2 statistic, with a higher number suggesting increased heterogeneity [17].

RESULTS

Characteristics of the Study in the Systematic Review

From 2004 to 2020, we identified 1713 studies that met the screening criteria for TA-TMA from 3 databases (MEDLINE, 423; Embase, 1229, CENTRAL, 61). After deduplication, 1434 studies were included for title and abstract screening, and 203 full-text studies were found to be relevant. Among these, 21 studies were selected for the final systematic review (Figure 1). The detailed reasons behind the exclusion of the 182 full-text studies are shown in Supplementary Table S3. The most common reason for exclusion was that the publication was an abstract only without a corresponding full-text peer-reviewed manuscript.

Study characteristics are summarized in Table 1. Among the 21 included studies, 3 reported differing incidences of TA-TMA in prespecified subgroups (Cutler 2005 [18], Willems 2010 [19], Khimani 2017 [20]); therefore, each subgroup population was treated as a separate study. Furthermore, 3 studies reported differing incidences of TA-TMA using different diagnostic criteria (Cho 2010 [6], Li 2019 [3], Schoettler 2020 [21]). In these scenarios, only the primary study definition was used in the overall pooled analysis; however, each study contributed multiple times to different subgroups when assessing the impact of diagnostic criteria. In total, 36,163 patients from 24

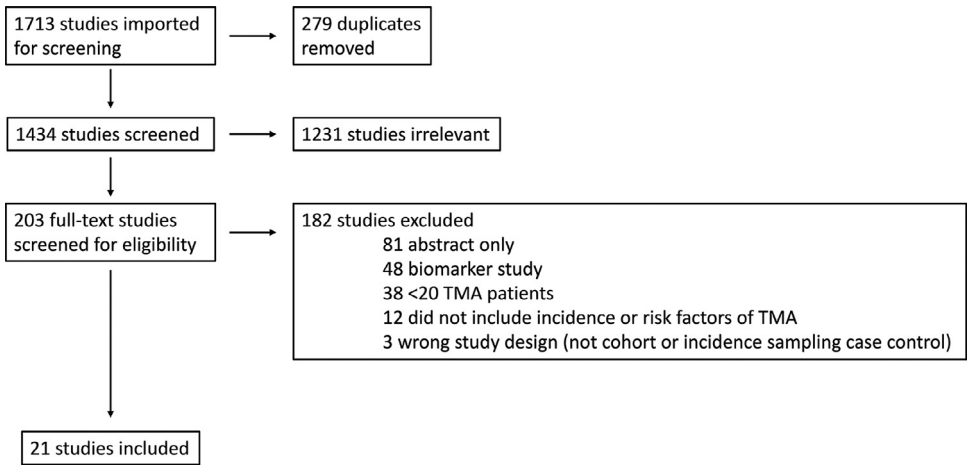

Figure 1. PRISMA flow diagram for study selection in the systematic review. The diagram shows each step of the systematic review, as well as the reasons for exclusion.

Table 1
Characteristics of Studies Included in the Systemic Review

Study	Country, Time Frame	N (N)	Median Age, yr	Male, %	Allogenic HCT, %	Malignant, %	Myeloablative Conditioning, %	Acute GVHD, II-IV, %	TMA, %	Onset, day	Follow-up, d
Cho (2010) [7]	South Korea, 2002-2006	672	34	54.3	100.0	84.3	66.3	35.3	12.6* 6.1† 2.5‡	47	1315
Cutler (2005) (non-SIR) [18]	US, 1997-2003	216	41	54.2	100.0		100.0	27.3	4.2	58	
Cutler (2005) (SIR) [18]	US, 1997-2003	111	40	56.8	100.0		100.0	22.5	10.8	25	
Dandoy (2021) [22]	US, 2016-2019	614	6.7	61.1	68.7	62.5	76.1	18.6	16.0	24	
Elfeky (2020) [27]	UK, 2013-2017	441	2.7	65.3	100.0	30.6	43.8	3.4	5.7	153	100
Epperla (2020) [24]	US, 2008-2016	23,665	49	58.9	100.0	88.1	56.4	38.4	2.8	90	1125
Gavriilaki (2018) [28]	Greece, 1990-2017	758	38	38.3	100.0	98.8	20.3	8.2	15.3	86	690
Hale (2005) [29]	US, 1992-1999	293	9.7	53.9	100.0	83.3	100.0	19.8	9.6	171	719
Jodele (2014) [23]	US, 2010-2011	100	6.1	57.0	90.0	26.0	48.0	62.0	39.0	32	365
Khimani (2017) (MTX/TAC) [20]	US, 2008-2013	414	52	23.4	100.0	96.4	53.4	72.9	14.7		730
Khimani (2017) (SIR/TAC) [20]	US, 2008-2013	293	56	32.8	100.0	99.3	52.9	63.5	6.1		730
Kraft (2019) [30]	Switzerland, 2006-2016	660	47	59.5	100.0	96.7	78.0	52.1	9.8	36	532
Li (2019) [3]	US, 2006-2015	2145	51	58.3	100.0	96.5	57.6		9.0* 3.3§	59	99
Martinez (2005) [25]	Switzerland, 1995-2002	221	35	55.2	100.0	96.4	82.4	53.8	30.8	27	791
Nakamae (2006) [31]	Japan, 1994-2004	123	38	53.7	100.0	98.4	61.0		17.9	33.5	
Oran (2007) [32]	US, 1998-2004	1219	47	60.6	100.0	100.0	46.8		5.4	67	833
Postalcioglu (2018) [33]	US, 2005-2015	1990	53	58.0	100.0	96.2	38.6	28.7	13.0	45	1466
Schoettler (2020) [21]	US, 2014-2018	307	8.5	63.5	66.8	33.9	44.6		20.2* 35.8¶ 2.6§	29	475
Shayani (2013) [34]	US, 2005-2007	177	46	55.4	100.0	100.0	40.1	50.3	16.9	32	1521
Shimoni (2004) [35]	Israel, 2000	147	43	59.2	100.0	100.0	42.9	37.4	15.0	30	
Uderzo (2006) [36]	Italy, 2000-2005	539	31	58.3	100.0	91.3	100.0	37.5	11.9	47	424
Willems (2010) (myeloablative) [19]	Belgium, 2000-2008	111	42	60.4	100.0	92.8	100.0	26.1	15.3	54	
Willems (2010) (non-MA) [19]	Belgium, 2000-2008	176	57	66.5	100.0	100.0	0	39.8	14.2	49	
Zeisbrich (2017) [37]	Germany, 2001-2014	771	53	61.1	100.0	98.7	19.6	25.6	5.3	54	1498

MTX indicates methotrexate; TAC, tacrolimus; SIR, sirolimus, non-MA, nonmyeloablative.
* Cho definition.
† BMT-CTN definition.
‡ IWG definition.
§ Clinical definition.
¶ Jodele definition.

unique populations among 21 published studies were included in the current systematic review. Studies from 10 different countries—the United States, Japan, Belgium, Germany, United Kingdom, South Korea, Greece, Switzerland, Israel, and Italy—were analyzed. The median number of participants per study was 361 (range, 100 to 23,665), with a median follow-up (reported in 17 studies) of 24 months (range, 3 to 50 months). The median age of participants was 42 years (range, 2.7 to 57 years), and males predominated (58%). With exception of 3 studies (Dandoy 2021 [22], Jodele 2014 [23], and Schoettler 2020 [21]), the cohorts included exclusively allogeneic HCT recipients. There was a strong correlation between younger median age of participants and higher proportion of nonmalignant diseases.

Among the studies included in the full-text review, multiple different diagnostic criteria were used for diagnosing TA-TMA (Table 2). The most widely used criteria included definitions from the BMT-CTN [4], IWG [5], Cho [6], Jodele [23], and provider/clinical diagnosis [24], as well as various study-specific definitions created out of convenience based on available retrospective data. Most of the definitions included schistocytosis (at various numbers and percentages), elevated lactate dehydrogenase (at various thresholds above upper limit of normal), thrombocytopenia (at various thresholds of count), and anemia (at various thresholds below lower limit of normal). Some studies excluded laboratory evidence of coagulopathy for disseminated intravascular coagulation or autoimmune hemolytic anemia. Only 4 studies relied on detailed chart review to exclude other causes or mimics of TA-TMA.

Risk of Bias and Publication Bias Assessment

The risk of bias assessment is shown in Supplementary Figure S1. Selection bias occurred in 5 studies that compared subpopulation rather than all consecutive patients post-transplantation. Bias in the measurement of outcomes was problematic in 8 studies, as the study definition was nonspecific in defining TA-TMA or was difficult to replicate (ie, 4 out of 7 criteria). Most studies did not report missing data, even though this would be expected in retrospective cohort studies. As shown in Supplementary Figure S2, the funnel plot demonstrated significant publication bias, even after exclusion of the largest study, Epperla (2020) [24].

At least 9 studies were outside the expected funnel plot range. Specifically, smaller studies (ie, less precise or with higher standard error) reported the largest effect size (higher incidence of TA-TMA) whereas larger studies (ie, more precise or with lower standard error) reported the smallest effect size (lower incidence of TA-TMA).

Overall and Subgroup Pooled Analysis on the Incidence of TA-TMA

The reported cumulative incidence of TA-TMA during early post-transplantation follow-up ranged from 3% to 39% across different studies, with a median time to onset of 47 days (range, 24 to 171 days). In the meta-analysis of proportion, the overall pooled incidence of TA-TMA across all studies from 2004 to 2020 was 12% (95% CI, 9% to 16%), with a high degree of heterogeneity (I^2 = 98%) (Figure 2). Notably, when a study reported multiple different diagnostic criteria, the primary criteria chosen by the authors were used for the overall pooled estimate.

When each diagnostic criterion was assessed as a subgroup, the pooled TA-TMA incidences were 3% (95% CI, 3% to 3%) in clinical diagnosis, 7% (95% CI, 2% to 16%) in IWG, 10% (95% CI, 6% to 14%) in BMT-CTN, 13% (95% CI, 9% to 18%) in Cho, 17% (95% CI, 5% to 35%) in Jodele, and 17% (95% CI, 12% to 22%) in study-specific criteria (Figure 2). Notably, the clinical diagnosis subgroup was the only one without significant heterogeneity (I^2 = 0%). The 3 studies that reported the lowest incidence of TA-TMA were Li (2019) (3%; n = 2145) [3], Epperla (2020) (3%, n=23,665) [24], and Schoettler (2020) [21] using the clinical diagnosis (3%; n = 307). The 3 studies that reported the highest incidence of TA-TMA were Martinez (2005) (31%; n = 221) [25], Jodele (2014) (39%; n = 100) [23], and Schoettler (2020) using the Jodele 4/7 criteria (36%; n = 307) [21].

In addition to diagnostic criteria, we performed additional subgroup analyses based on the number and median age of participants. First, we assessed whether study size impacted TA-TMA incidence as larger studies provided higher precision of estimates. Using the median number of participants from the included studies, we divided studies into those with ≥400 patients (n = 12) versus those with <400 patients (n = 12). In this subgroup analysis, the reported TA-TMA incidence was 10% (95% CI, 6% to 14%) in large studies (n ≥400) versus 16% (95% CI, 11% to 21%) in small studies (n <400) (Supplementary Figure S3). We then subdivided the studies by age group into predominantly adults (median age ≥30 years; n = 19) and predominantly children and young adults (median age <30 years; n = 5). The pooled incidence was 11% (95% CI, 8% to 15%) in the adult studies versus 16% (95% CI, 9% to 25%) in the pediatric/young adult studies (Supplementary Figure S4).

Finally, we performed a subgroup analysis based on the proportion of malignant versus nonmalignant diseases, and the results were nearly identical to the previous analysis by age (data not shown). Additional exploratory subgroup analyses by country, year of HCT, sex, and conditioning intensity did not contribute significantly to the heterogeneity of disease incidence across the studies.

Risk Factors for TA-TMA

A total of 8 different risk factors were reported in multivariable analyses from more than 3 studies (Table 3). The most common risk factor, reported in 14 studies, was preceding grade II-IV acute GVHD. Preceding infection, mismatched donor, prior HCT, and myeloablative conditioning were each identified as a risk factor in 5 studies. Sirolimus-containing GVHD prophylaxis regimen or high sirolimus trough level, female sex, and older age were observed in 3 to 4 studies, but several other studies explicitly refuted these associations.

DISCUSSION

In the current systematic review and meta-analysis from 2004 to 2020, we found 21 cohort studies with a total of 36,163 patients that reported a measurable incidence of and risk factors for TA-TMA. The overall pooled incidence for TA-TMA was 12% (95% CI, 9% to 16%), and the difference in diagnostic criteria used to define the disease was the most significant contributor to the inter-study heterogeneity. Furthermore, we detected a publication bias such that studies with fewer participants reported the highest incidence of the disease. High-grade or refractory acute GVHD and systemic infection (especially viral) were the most consistent time-varying risk factors for TA-TMA. Mismatched donor, multiple prior HCTs, and myeloablative conditioning were the most common baseline risk factors. Overall, our systematic review of the literature over the last 17 years suggests that TA-TMA is becoming increasingly recognized as a significant post-transplantation complication; however, it remains a relatively uncommon disease with multiple different triggers of endothelial injury.

Table 2
Details of the Diagnostic Criteria used in each Study

Study	Diagnostic Criteria	Diagnostic Criteria Details	Schistocytes Required	End-Organ Damage	Clinical Diagnosis
Cho (2010)	Cho	Schisto ≥2/HPF, LDH >ULN, Plt <50 or >50% drop, Hb "decreased", DAT negative, PT/PTT normal, haptoglobin "decreased"	Yes	No	No
Cho (2010)	BMT-CTN	Schisto ≥2/HPF, LDH >ULN, Cr ≥2 times baseline and/or neurologic dysfunction without other explanations, DAT/IAT negative	Yes	Yes	No
Cho (2010)	IWG	Schisto ≥4%, LDH >ULN, Plt <50 or >50% drop, Hb "decreased," haptoglobin "decreased"	Yes	No	No
Cutler (2005) (non-SIR)	BMT-CTN	Schisto ≥2/HPF, LDH >ULN, no DIC, Cr ≥2 times baseline	Yes	Yes	No
Cutler (2005) (SIR)	BMT-CTN	Schisto ≥2/HPF, LDH >ULN, no DIC, Cr ≥2 times baseline	Yes	Yes	No
Dandoy (2021)	Jodele (4/7)	Schisto "any," LDH >ULN, Plt "decreased or requiring transfusion," Hb "decreased or requiring transfusion," HTN >99th percentile or requiring ≥2 antihypertensive meds, proteinuria ≥30 mg/dL on UA, sC5b9 ≥244 mg/dL [4/7], or histology on biopsy	No	No	No
Elfeky (2020)	Jodele (5/7)	Schisto "any," LDH >ULN, Plt "decreased or requiring transfusion," Hb "decreased or requiring transfusion," HTN >99th percentile or requiring ≥2 antihypertensive meds, proteinuria ≥30 mg/dL on UA, sC5b9 ≥244 mg/dL [5/7], or histology on biopsy	No	No	No
Epperla (2020)	Clinical	Clinical diagnosis	Yes	No	Yes
Gavriilaki (2018)	IWG	Schisto >4%, LDH >ULN, Plt "decreased," Hb "decreased," haptoglobin "decreased"	Yes	No	No
Hale (2005)	Cho	Schisto "any," LDH >ULN, Plt "low," DAT negative, no DIC	Yes	No	No
Jodele (2014)	Cho	Schisto≥1/HPF, LDH >ULN, Plt <50 or >50% drop, Hb <LLN or requiring transfusion (4/4 in 24 hr, 2+ times), DAT negative, PT/PTT normal	Yes	No	No
Khimani (2017) (MTX/TAC)	BMT-CTN	Schisto ≥2/HPF, LDH >ULN, Cr ≥2 times baseline and/or neurologic dysfunction without other explanation, DAT/IAT negative	Yes	Yes	No
Khimani (2017) (SIR/TAC)	BMT-CTN	Schisto ≥2/HPF, LDH >ULN, Cr ≥2 times baseline and/or neurologic dysfunction without other explanation, DAT/IAT negative	Yes	Yes	No
Kraft (2019)	Cho	Schisto >2/HPF, LDH>ULN, Plt <50 or >50% drop, haptoglobin "decreased," DAT negative, PT/PTT normal	Yes	No	No
Li (2019)	Cho	Schisto >2/HPF, LDH >2 times ULN, Plt <50 or >50% drop, Hb <LLN (4/4 in 24 hr, 2+ times), DAT negative (if checked), no DIC (ISTH definition), no pretransplantation disease relapse, no other more apparent cause	Yes	No	No
Li (2019)	Clinical	Clinical diagnosis	Yes	No	Yes
Martinez (2005)	Study-specific	Schisto ≥2/HPF, LDH >300, total bilirubin ≥2.5, Hb ≥1 drop	Yes	No	No
Nakamae (2006)	Study-specific	Schisto ≥1.2%, LDH ≥500 [2/2], "hemolysis," Plt <150, Cr >1.5 or 1.5 times baseline, neurologic dysfunction, temperature >38 °C [2/5]	Yes	No	No
Oran (2007)	Cho	Schisto ≥1/HPF, LDH ≥1.5 baseline, Hb "drop or increased transfusion," Plt <50 or 50% drop (haptoglobin <LLN, DAT negative, PT/PTT normal) [not necessary]	Yes	No	No
Postalcioglu (2018)	Study-specific	Schisto "any" or nRBC on 2+ smears, LDH >2 times ULN, Plt <50 or >50% drop, Cr >1.5 times baseline	No	Yes	No
Schoettler (2020)	Cho	Schisto "any," LDH >ULN, Plt "decreased or requiring transfusion," Hb "decreased or requiring transfusion," DAT negative, PT/PTT normal	Yes	No	No
Schoettler (2020)	Jodele (4/7)	Schisto "any," LDH >ULN, Plt "decreased or requiring transfusion," Hb "decreased or requiring transfusion," HTN >99th percentile or requiring ≥2 anti-HTN meds, proteinuria ≥30 mg/dL on UA, sC5b9 ≥244 mg/dL	No	No	No
Schottler (2020)	Clinical	Clinical diagnosis	Yes	No	Yes
Shayani (2013)	Study-specific	Schisto "any" or nRBC on 2+ smears, LDH >2 times ULN, Plt <50 or >50% drop, Cr >1.5 times baseline	No	Yes	No
Shimoni (2004)	Study-specific	Schisto "any," Plt "decreasing," LDH>ULN	Yes	No	No
Uderzo (2006)	Study-specific	Schisto >2%, LDH ≥2 times ULN, Hb <8, Plt <20, reticulocytes >20, elevated LDH/Plt ratio [4/6]; Cr 2 times baseline, CNS involvement, bleeding without DIC [2/3]	No	Yes	No
Willems (2010) (myeloablative)	BMT-CTN	Schisto ≥2/HPF, LDH >ULN, Cr ≥2 times baseline, and/or neurologic dysfunction without other explanations	Yes	No	No
Willems (2010) (non-MA)	BMT-CTN	Schisto ≥2/HPF, LDH >ULN, Cr ≥2 times baseline, and/or neurologic dysfunction without other explanations	Yes	No	No
Zeisbrich (2017)	IWG	Schisto ≥4%, LDH ≥1.5 times baseline or ≥400, Plt <50 or >50% drop, Cr ≥1.5 times baseline	Yes	Yes	No

Schisto indicates schistocyte; HPF, high-power field; LDH, lactate dehydrogenase; ULN, upper limit of normal; Plt, platelet count; Hb, hemoglobin; DAT, direct antiglobulin test; PT, prothrombin time; PTT, partial thromboplastin time; Cr, creatinine; IAT, indirect antiglobulin test; DIC, disseminated intravascular coagulation; UA, urinalysis; HTN, hypertension; LLN, lower limit of normal; ISTH, International Society on Thrombosis and Haemostasis; nRBC, nucleated red blood cells.

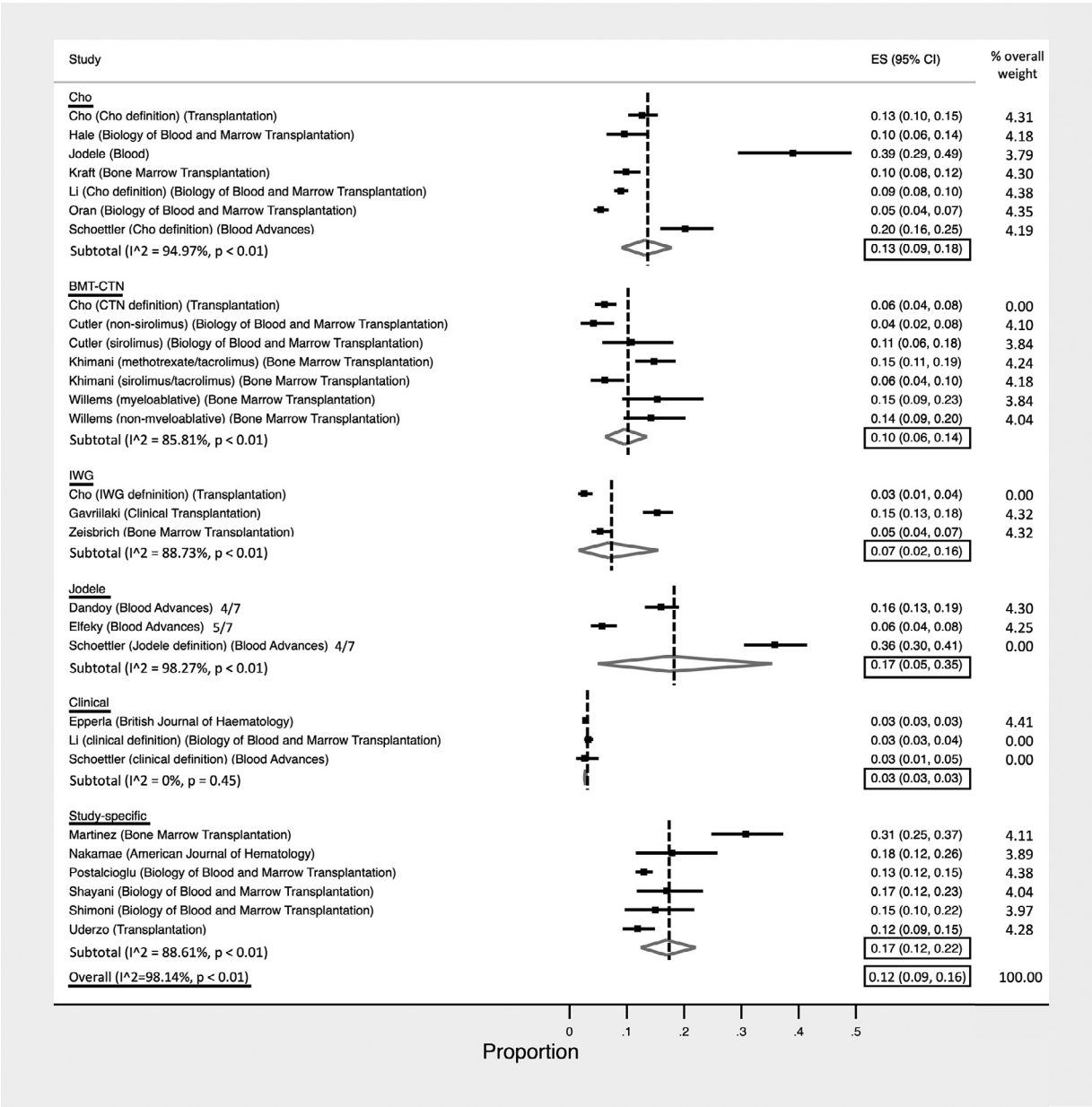

Figure 2. Meta-analysis of overall pooled incidence of TA-TMA and incidence by different diagnostic criteria. The forest plot shows the pooled incidence of TA-TMA across all included studies organized by different diagnostic criteria. For studies that reported multiple TA-TMA outcomes based on different diagnostic criteria (Cho, Schoettler, Li), only the primary outcome of the study was included in the overall weight estimation.

In the systematic review published by George and Selby in 2004 [26], the reported incidence of TA-TMA ranged from 0.5% to 63.6%. Since then, that range has narrowed to 3% to 39%, and more precisely to a 95% CI of 9% to 16% with a pooled incidence of 12% using modern statistical estimation. It is important to recognize that TA-TMA has never had a uniform set of diagnostic criteria. The difficulty associated with TA-TMA diagnosis is also seen in several other rare hematologic diseases, such as autoimmune hemolytic anemia, sinusoidal obstruction syndrome, and even disseminated intravascular coagulation. These clinical syndromes can be readily recognized by experienced hematologists, yet they do not have a clear diagnostic gold standard clinical rule or laboratory test. We noted this phenomenon in the current systematic review. All studies that relied on provider diagnosis had the lowest yet the most consistent incidence of 3% in the early post-transplantation window. In contrast, studies that reported the highest incidence of TA-TMA of 36% to 39% exclusively used the most recent Jodele diagnostic criteria that required only 4 out of 7 laboratory parameters. As shown in Table 2, some of these studies did not even require the presence of schistocytes or thrombocytopenia, which should be the cornerstone for defining microangiopathic hemolytic anemia and TMA.

Although clinicians must remain vigilant to recognize rare and potentially severe complications such as TA-TMA, this must be balanced with diagnostic criteria of sufficient sensitivity and specificity to avoid the risk of overdiagnosis. Appropriately sensitive and specific clinical disease definition is critical for both epidemiologic disease surveillance and inclusion/exclusion for ongoing clinical trials, particularly given the extraordinary cost of current best available therapies for TA-TMA.

Table 3
Risk Factors for the Development of TA-TMA found in Multivariable Analyses in Multiple Studies

Risk Factors Reported on Multivariable Analysis	Studies
Concomitant/previous aGVHD (*severe aGVHD grade II-IV; **refractory aGVHD)	Cho (2010)*, Cutler (2005)*, Elfeky (2020)*, Epperla (2020)*, Gavriilaki (2018), Li (2019)*, Nakamae (2006)*, Oran (2007)*, Schoettler (2020)*, Shayani (2013)*, Shimoni (2004), Uderzo (2006)*, Willems (2010)*, Zeisbrich (2017)**
Mismatched donor	Cho (2010), Epperla (2020), Li (2019), Martinez (2005), Oran (2007)
Concomitant/previous infection	Cho (2010), Gavriilaki (2018), Li (2019), Schoettler (2020), Elfeky (2020)
More than 1 previous HCT	Elfeky (2020), Epperla (2020), Li (2019), Schoettler (2020), Shimoni (2004)
Myeloablative conditioning	Epperla (2020), Gavriilaki (2018), Li (2019), Nakamae (2006), Shayani (2013), Uderzo (2006)
Sirolimus regimen/high-dose	Cutler (2005), Epperla (2020), Li (2019), Shayani (2013)
Female sex	Martinez (2005), Oran (2007), Uderzo (2006), Zeisbrich (2017)
Older age	Cho (2010), Martinez (2005), Willems (2010)

aGVHD indicates acute graft-versus-host disease.

In addition to variations in diagnostic criteria, we also noted several other factors that drove the heterogeneity of the included studies. Although not statistically significant, smaller studies, pediatric cohorts, and nonmalignant disease all trended toward higher TA-TMA rates; however, these factors also were often strongly correlated. This led us to examine adjusted risk factors reported in multiple studies. Indeed, post-transplantation predictors, such as preceding acute GVHD or systemic infection, had the most consistent and strongest association with TA-TMA, whereas pretransplantation predictors, such as mismatched donor, myeloablative conditioning, and more than 1 prior HCT, had more modest strengths of association. Similar to the previous systematic review published in 2004 [8], although age was reported as a risk factor in 3 studies, most studies, including the study from the Center for International Bone and Marrow Transplantation Research that included all age groups, refuted that association. [24] It is conceivable that many of these pretransplantation risk factors predispose patients to develop either GVHD or infection, which in turn causes endothelial injury and the development of TA-TMA.

Our current study has limitations inherent to pooling observational studies. First, given the notable differences in diagnostic criteria for outcome reporting across the studies (ie, bias in measurement of outcomes), there was significant heterogeneity in the pooled estimate of the overall incidence. Although we explored the cause of this heterogeneity further with subgroup analysis, we could not fully account for it, and thus our meta-analysis should be interpreted with caution. Second, the included studies had significant variation in the number of participants, ranging from 100 to 23,665. To mitigate the risk of overweighting a single study, we used a random-effects model instead of a fixed-effects model and excluded the Center for International Bone and Marrow Transplantation Research study from the funnel plot for publication bias assessment. Third, the exclusion of small case series that reported very few TA-TMA patients made the data extraction more manageable but could have introduced additional selection bias. Fourth, very few published prospective cohort studies relied on traditional TA-TMA diagnostic criteria. Future systematic reviews should focus on ongoing prospective cohort and interventional studies. Finally, our meta-analysis represented an aggregate participant level, because we did not have access to individual patient-level data. This shortcoming limited our ability to perform more in-depth meta-regression analyses.

In conclusion, the overall pooled incidence of TA-TMA was 12% among a highly heterogeneous allogeneic HCT recipient population from observational cohort studies published between 2004 and 2020. The diagnostic criteria used was the single most important driver of disease incidence. Despite the potential limitations, consistent risk factors for TA-TMA included preceding acute GVHD, systemic infection, prior HCT, mismatched donor, and myeloablative conditioning. Future studies should focus on risk- stratifying the subset of TA-TMA patients who would benefit from therapeutic intervention.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.01.009.

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