Clinical Features and Outcome of Thrombotic Microangiopathies: Comparison between Patients with and without Malignancy

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Abstract

Thrombotic microangiopathy (TMA) is an uncommon complication of cancers, related to the malignancy itself, antineoplastic drugs, or hematopoietic stem cell transplant. It was reported mostly as case series but large data are lacking. We used the large U.S. MarketScan database to compare TMA between patients with and without malignancy. Adult patients hospitalized between 2005 and 2014 with a diagnosis of TMA were included; cancer patients were defined by a diagnosis of cancer within 1 year prior to or during the admission with TMA. Associated inpatient diagnoses, procedures, hospital mortality, and long-term survival were collected. We included 3,227 patients; 617 (19.1%) had cancer (age 54 [44–60] years, 58% female), which was a new diagnosis for 23% of patients. Two-thirds of cancer patients had solid tumors (mostly pancreas, lung, breast, colorectal, and hepatobiliary, half of them metastatic) and one-third had hematological malignancies (lymphoma, acute leukemia, and multiple myeloma); TMA patients with cancer were older, more often men, had more noncancer-related comorbidities, and developed more sepsis and coagulopathy than TMA patients without cancer. Hospital mortality was significantly higher in cancer patients (16.6% vs. 6.1%, $p < 0.001$) and reached 30% in transplant recipients; malignancy was an independent risk factor for hospital mortality in multivariate analysis and sensitivity analyses excluding patients with metastases or patients who did not undergo plasmapheresis led to similar results. Malignancy was also associated with decreased long-term survival.

Keywords
- thrombotic microangiopathy
- cancer
- hematological malignancy
- mortality

Introduction

Thrombotic microangiopathies (TMAs) are characterized by microangiopathic hemolytic anemia, thrombocytopenia, and result in ischemic organ damage of various degree and location (most commonly brain and kidney).[1] TMA include two main entities: thrombotic thrombocytopenic purpura (TTP) caused by a deficiency in ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) with subsequent formation of prothrombotic ultra-large von Willebrand factor multimers, and hemolytic and uremic syndrome (HUS), either caused by Shiga toxin-producing *Escherichia coli* (typical HUS) or associated with genetic or acquired disorders of regulatory components of the complement system (atypical HUS).[1]

The association between cancer and TMA is well known,[2] as a consequence of either the cancer itself,[3] the chemotherapy,[4] or hematopoietic stem cell transplant (HSCT).[5] Available data

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mostly come from case reports or small series; Lechner and Obermeier collected and analyzed 168 cases published between 1979 and 2012[3]: 90% of cases were solid tumors (mostly gastric, breast, prostate, lung) and 90% of them were metastatic; only a minority had typical features of TTP or HUS, and disseminated intravascular coagulation (DIC) and respiratory complications were more frequent than reported in nonmalignant TMA. These cases usually did not respond to plasma therapy and carried a poor prognosis with 50% mortality at 1 month.

There is a potential publication bias associated with case reports and series and no large-scale, population-based study has investigated cancer-related TMA. The diagnosis, management, and prognosis of noncancer-related TMA have also improved since most of these cases were published,[6,7] but whether this translates into a better prognosis of cancer-related TMA is unknown.

The objective of this study was to use a large U.S. database to compare TMA between patients with and without malignancy and to assess the prognosis of cancer-related TMA in the modern era.

Methods

This retrospective cohort study used data from the Truven Health MarketScan database to describe the characteristics of patients diagnosed with TMA. The Penn State Institutional Review Board approved this research and waived informed consent for this retrospective study (study number 6364). The database is a commercially available health insurance claims database. It includes claims data for a sample of more than 245 million privately insured people in all 50 U.S. states, including demographic characteristics, health care utilization and costs, dates of service, diagnosis codes, and procedure codes. The data represent claims from clinicians, hospitals, and pharmacies that have been adjudicated for payment and are obtained directly from a convenience sample of large employers and health plans that agree to participate in the database. MarketScan does not include patients on Medicare ($\geq$ 65-year-old). Truven Health has a quality-control process to verify that the data meet criteria for quality and completeness. This database has been used in multiple other studies, including studies examining complications and follow-up care after health care procedures.[8,9]

The study population included all adults ($>$ 18-year-old) with hospital inpatient admissions associated with a International Classification of Diseases 9th Edition (ICD-9) diagnosis code of TMA (446.6) or HUS (283.11) between 2005 and 2014.

Data Collected

For patients with multiple admissions, only the first inpatient admission with a diagnosis of TMA or HUS was included, to ensure independence of observations. Demographics, Charlson Comorbidity Index[10] based on ICD-9 diagnoses within 1 year prior to admission, ICD-9 principal and secondary diagnoses (up to 15 per admission), procedures codes (up to 15 per admission), and discharge status were collected. To assess survival status over time, we used discharge status for the last inpatient admission (regardless of diagnoses) as well as physician office visits and outpatient prescription fillings (whichever the latest). Patients with malignancy or metastases were defined based of the presence of corresponding ICD-9 codes (140–209, 235–239) either in the computed Charlson Comorbidity Index or during the inpatient admission.

To analyze diagnoses associated with TMA, specific ICD-9 codes (see ►**Supplementary Table S1**, available in the online version) were used to define hematopoietic stem cell transplant (HSCT), autoimmune diseases, acute kidney injury, encephalopathy, epilepsy, transient ischemic attack, stroke, sepsis and severe sepsis, acute respiratory failure, disseminated intravascular coagulation (DIC), cardiogenic shock, acute coronary syndrome, and cardiac arrest. Similarly, ICD-9 procedure and Current Procedural Terminology codes were used to define mechanical ventilation, renal replacement therapy, HSCT, and therapeutic plasma exchange (TPE).

Statistical Analysis

Quantitative variables were described as median (interquartile range) and were compared between groups using the nonparametric Wilcoxon rank-sum test. Qualitative variables were described as frequency (percentages) and were compared between groups using Fisher's exact test. To analyze hospital mortality in the whole population, variables associated with outcome with $p < 0.15$ in univariate analysis were entered into a backward stepwise regression to build the final logistic regression model. Linearity for quantitative variables, outliers, collinearity, and goodness of fit for the final model were carefully checked. A second logistic regression model was developed to determine predictors of hospital mortality in the subset of patients with malignancy using the same approach. Long-term survival was described with Kaplan–Meir curves and log rank test was used to compare groups. Sensitivity analyses including only patients who underwent TPE, only cancer patients without metastases, and only patients with ICD-9 cancer diagnoses recorded during inpatient admission were performed.

Results

Population Characteristics

During the 10-year study period, 3,227 patients (age 46 [35–56] years, 65% female) in the database were hospitalized with a diagnosis of TMA (►**Table 1**). Regarding the type of TMA, 885 (27.4%) patients had a diagnosis of HUS and 880 (27.3%) patients had no diagnosis of HUS and underwent TPE (the combination of criteria being used as a surrogate for TTP[11]). The most frequent complications during admission were acute kidney injury (47%), acute respiratory failure (15.5%), encephalopathy (13%), and sepsis (9.4%); mechanical ventilation and renal replacement therapy were required in 9.1 and 16.6% of patients, respectively. Hospital mortality was 8.1%.

Among these patients, 617 (19.1%) had a diagnosis of malignancy (age 54 [44–60] years, 58% female) and 24% ($n = 149$) of them had no documented diagnosis of malignancy prior to the admission, suggesting either a new diagnosis or relapse/recurrence.

Table 1 Population characteristics

	Patients ($n = 3,227$)
Age (y)	46 (35–56)
Female gender, *n* (%)	2,110 (65.4)
Comorbidities	
Myocardial infarction, *n* (%)	90 (2.8)
Congestive heart failure, *n* (%)	201 (6.2)
Peripheral vascular disease, *n* (%)	155 (4.8)
Cerebrovascular disease, *n* (%)	264 (8.2)
Dementia, *n* (%)	5 (0.2)
Chronic obstructive pulmonary disease, *n* (%)	359 (11.1)
Connective tissue disease, *n* (%)	239 (7.4)
Peptic ulcer disease, *n* (%)	44 (1.4)
Mild chronic liver disease, *n* (%)	269 (8.3)
Diabetes mellitus, *n* (%)	499 (15.5)
Diabetes mellitus with complications, *n* (%)	137 (4.2)
Hemiplegia, *n* (%)	33 (1.0)
Chronic kidney disease, *n* (%)	535 (16.6)
Cancer, *n* (%)	468 (14.5)
Severe chronic liver disease, *n* (%)	34 (1.1)
Metastases, *n* (%)	174 (5.4)
HIV, *n* (%)	43 (1.3)
Charlson Comorbidity Index	
0	1,489 (46.1)
1–2	929 (28.8)
3–4	435 (13.5)
≥ 5	374 (11.6)
Inpatient diagnoses	
History or complications of hematopoietic stem cell transplant, *n* (%)	42 (1.3)
Malignancy, *n* (%)	617 (19.1)
Hemolytic uremic syndrome, *n* (%)	885 (27.4)
Thrombotic thrombocytopenic purpura[a], *n* (%)	880 (27.3)
Autoimmune disease, *n* (%)	187 (5.8)
Acute kidney injury, *n* (%)	1,517 (47.0)
Encephalopathy, *n* (%)	418 (13.0)
Epilepsy, *n* (%)	170 (5.3)
Transient ischemic attack, *n* (%)	84 (2.6)
Stroke, *n* (%)	207 (6.4)
Sepsis, *n* (%)	302 (9.4)
Severe sepsis, *n* (%)	140 (4.3)
Acute respiratory failure, *n* (%)	501 (15.5)
Disseminated intravascular coagulation, *n* (%)	110 (3.4)
Cardiogenic shock, *n* (%)	29 (0.9)
Acute coronary syndrome, *n* (%)	130 (4.0)
Cardiac arrest, *n* (%)	46 (1.4)
Inpatient procedures	
Invasive mechanical ventilation, *n* (%)	294 (9.1)
Renal replacement therapy, *n* (%)	535 (16.6)
Hematopoietic stem cell transplant, *n* (%)	17 (0.5)
Therapeutic plasma exchange, *n* (%)	1,156 (35.8)
Hospital mortality, *n* (%)	244 (8.1)

Abbreviation: HIV, human immunodeficiency virus.
[a]The combination of a procedure code for therapeutic plasma exchange and the absence of diagnosis code for hemolytic uremic syndrome was considered as a surrogate for thrombotic thrombocytopenic purpura.

Comparison of TMA Patients with and without Malignancy

►**Table 2** provides a comparison of the characteristics of TMA patients with and without malignancy: cancer patients were older, more frequently male, and had more noncancer comorbidities, as attested by higher noncancer Charlson Comorbidity Index, and more frequent congestive heart failure, chronic obstructive pulmonary disease, chronic liver disease, and diabetes mellitus. Autoimmune diseases were less frequent in this group who presented more often sepsis and DIC during admission, whereas the prevalence of other common complications of TMA, like acute kidney injury, neurological and cardiac events, was not different between patients with and without cancer. Likewise, requirement for invasive mechanical ventilation and renal replacement therapy was not different between the two groups whereas cancer patients less frequently underwent TPE.

Effect of Malignancy on Mortality

Hospital mortality was significantly higher in cancer patients (16.6% vs. 6.1%, $p < 0.001$). In the multivariate logistic regression model, malignancy was independently associated with hospital mortality (odds ratio [OR] 2.602, 95% confidence interval [CI] 1.856–3.634, $p < 0.001$) along with age, chronic liver and pulmonary disease, encephalopathy, sepsis, acute coronary syndrome, and mechanical ventilation; hemolytic uremic syndrome and TPE were on the contrary associated with decreased mortality (►**Table 3**). The association between malignancy and hospital mortality remained significant in sensitivity analyses excluding patients with metastases (OR 2.442, 95% CI 1.646–3.583, $p < 0.001$), patients who did not undergo TPE (OR 2.025, 95% CI 1.020–3.910, $p = 0.04$), or patients whose cancer was documented as part of the Charlson Comorbidity Index but not during the inpatient admission (OR 2.617, 95% CI 1.823–3.732, $p < 0.001$). As evidenced by the Kaplan–Meier curves in ►**Fig. 1**, the long-term survival of

Table 2 Comparison of TMA patients with and without malignancy

	No malignancy ($n = 2,610$)	Malignancy ($n = 617$)	*p*-Value
Age (y)	44 (33–55)	54 (44–60)	< 0.001
Female gender, *n* (%)	1,750 (67.0)	360 (58.3)	< 0.001
Comorbidities			
Myocardial infarction, *n* (%)	71 (2.7)	19 (3.1)	0.626
Congestive heart failure, *n* (%)	144 (5.5)	57 (9.2)	< 0.001
Peripheral vascular disease, *n* (%)	126 (4.8)	29 (4.7)	0.894
Cerebrovascular disease, *n* (%)	207 (7.9)	57 (9.2)	0.287
Dementia, *n* (%)	5 (0.2)	0 (0.0)	0.277
Chronic obstructive pulmonary disease, *n* (%)	269 (10.3)	90 (14.6)	0.002
Connective tissue disease, *n* (%)	204 (7.8)	35 (5.7)	0.067
Peptic ulcer disease, *n* (%)	28 (1.1)	16 (2.6)	0.003
Mild chronic liver disease, *n* (%)	163 (6.2)	106 (17.2)	< 0.001
Diabetes mellitus, *n* (%)	376 (14.4)	123 (19.9)	< 0.001
Diabetes mellitus with complications, *n* (%)	112 (4.3)	25 (4.1)	0.791
Hemiplegia, *n* (%)	23 (0.9)	10 (1.6)	0.101
Chronic kidney disease, *n* (%)	426 (16.3)	109 (17.7)	0.419
Cancer, *n* (%)	0 (0.0)	468 (75.9)	< 0.001
Severe chronic liver disease, *n* (%)	23 (0.9)	11 (1.8)	0.049
Metastases, *n* (%)	0 (0.0)	174 (28.2)	< 0.001
HIV, *n* (%)	31 (1.2)	12 (1.9)	0.140
Charlson Comorbidity Index excluding cancer variables			< 0.001
0	1,412 (54.1)	238 (38.6)	
1–2	772 (29.6)	252 (40.8)	
3–4	292 (11.2)	87 (14.1)	
≥ 5	134 (5.1)	40 (6.5)	
Inpatient diagnoses			
Hemolytic uremic syndrome, *n* (%)	721 (27.6)	164 (26.6)	0.601
Autoimmune disease, *n* (%)	168 (6.4)	19 (3.1)	0.001
Acute kidney injury, *n* (%)	1,225 (46.9)	292 (47.3)	0.861
Encephalopathy, *n* (%)	336 (12.9)	82 (13.3)	0.782
Epilepsy, *n* (%)	144 (5.5)	26 (4.2)	0.192
Transient ischemic attack, *n* (%)	72 (2.8)	12 (1.9)	0.254
Stroke, *n* (%)	174 (6.7)	33 (5.3)	0.229
Sepsis, *n* (%)	225 (8.6)	77 (12.5)	0.003
Severe sepsis, *n* (%)	107 (4.1)	33 (5.3)	0.171
Acute respiratory failure, *n* (%)	393 (15.1)	108 (17.5)	0.13
Disseminated intravascular coagulation, *n* (%)	77 (3.0)	33 (5.3)	0.003
Cardiogenic shock, *n* (%)	21 (0.8)	8 (1.3)	0.244
Acute coronary syndrome, *n* (%)	110 (4.2)	20 (3.2)	0.269
Cardiac arrest, *n* (%)	38 (1.5)	8 (1.3)	0.764
Inpatient procedures			
Invasive mechanical ventilation, *n* (%)	231 (8.9)	63 (10.2)	0.291
Renal replacement therapy, *n* (%)	438 (16.8)	97 (15.7)	0.524
Therapeutic plasma exchange, *n* (%)	964 (36.9)	192 (31.1)	0.007
Hospital mortality, *n* (%)	149 (6.1)	95 (16.6)	< 0.001

Abbreviations: HIV, human immunodeficiency virus; TMA, thrombotic microangiopathy.

Table 3 Summary of the multivariate logistic regression model analyzing hospital mortality

Variable	Odds ratio	95% Confidence interval	*p*-Value
Age (y)	1.016	1.003–1.029	0.017
Hemolytic uremic syndrome	0.544	0.368–0.788	0.002
Chronic obstructive pulmonary disease	1.858	1.264–2.695	0.001
Chronic liver disease	1.785	1.162–2.689	0.007
Hematopoietic stem cell transplant	2.123	0.952–4.499	0.056
Encephalopathy	1.689	1.178–2.396	0.004
Sepsis	3.386	2.365–4.810	< 0.001
Acute coronary syndrome	2.172	1.256–3.644	0.004
Mechanical ventilation	7.372	5.300–10.245	< 0.001
Therapeutic plasma exchange	0.612	0.437–0.848	0.004
Malignancy	2.602	1.856–3.634	< 0.001

patients without cancer was higher than the survival of patients with cancer and no metastases and patients with metastatic cancer ($p < 0.0001$).

Subset of Patients with Malignancy

Out of 617 patients with malignancy, 498 had an ICD-9 code for malignancy documented during the admission for TMA. Among them, 318 (64%) had solid tumors and 180 (36%) hematological malignancy. About 55% of patients with solid tumors had metastases. History or complications of HSCT were documented in 7% ($n = 42$), and HSCT was performed during the same inpatient admission in 3% ($n = 17$). Regarding the type of TMA, 27% ($n = 164$) of cancer patients had a diagnosis of HUS and 22% ($n = 136$) had no diagnosis of HUS and underwent TPE, as a possible surrogate for TTP[11]; hospital mortality was not different between these two groups (11.0% vs. 11.8%, $p = 0.83$). ►**Supplementary Table S2** (available in the online version) details the main characteristics of patients for whom the cancer location was available: the most frequent malignancies associated with TMA were by order of importance non-Hodgkin lymphoma ($n = 50$), myeloid leukemia ($n = 46$), pancreas ($n = 34$), lung ($n = 33$), breast ($n = 32$), lymphoid leukemia ($n = 30$), multiple myeloma ($n = 24$), Hodgkin lymphoma ($n = 15$), colorectal ($n = 15$), and hepatobiliary ($n = 13$) cancers. The hospital mortality was 17% and 14% for patients with hematological malignancies and solid tumors, respectively ($p = 0.51$), but reached 30% in patients with HSCT. In multivariate logistic

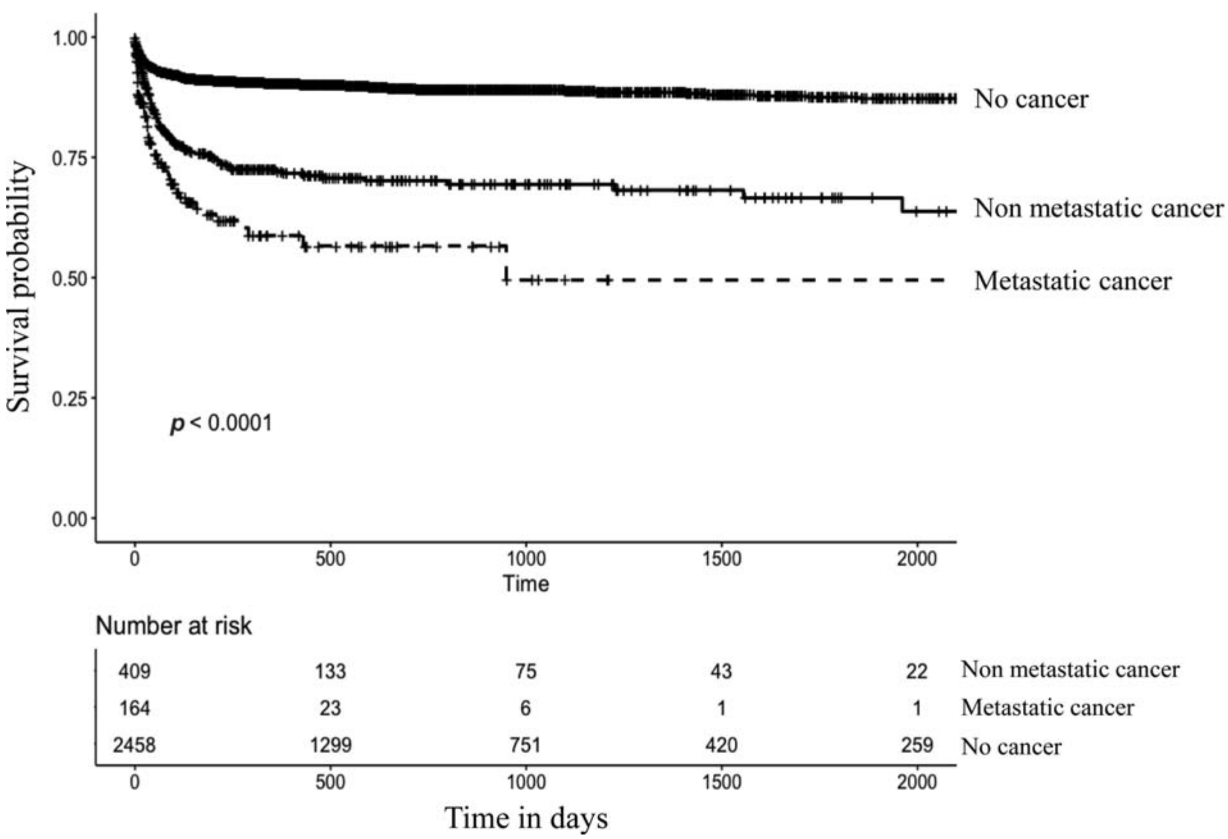

Fig. 1 Kaplan–Meier survival curves, starting at the day of admission with thrombotic microangiopathy (TMA), for patients with no cancer, cancer without metastases, and metastatic cancer. The log-rank test showed a statistically significant difference in survival between the three groups ($p < 0.0001$).

regression, variables associated with hospital mortality were sepsis (OR 3.850, 95% CI 2.102–6.996, $p < 0.001$) and mechanical ventilation (OR 6.950, 95% CI 3.737–13.043, $p < 0.001$), whereas TPE was protective (OR 0.509, 95% CI 0.275–0.900, $p = 0.02$).

Discussion

The main findings of this study were that in a large U.S. database, approximately 20% of the patients admitted with TMA had malignancy; two-thirds of cancer patients had solid tumors (half of them metastatic) and one-third hematological malignancies; their hospital mortality was 17% overall but reached 30% in patients with HSCT. Malignancy was an independent risk factor for hospital mortality in the population of TMA patients.

There is no solid data to our knowledge about the incidence of TMA in cancer patients. This was not the objective of this study; however, based on the number of patients with a new cancer diagnosis in the database during the study period we estimate that less than 0.5% of cancer patients developed TMA. This incidence was likely extremely low a few decades ago (Lechner and Obermeier for instance reported no TMA in a series of 2,046 patients with metastatic breast cancer[3]); however, it might be higher nowadays as therapeutic agents known to be associated with TMA (proteasome or vascular endothelial growth factor inhibitors for instance)[4] have been since introduced or more widely used.

More data are available regarding the prevalence of cancer in patients with TMA: in the largest series of patients with TTP, approximately 10% had cancer and 3.5% had undergone transplantation.[12] We observed a higher prevalence of cancer in our population of TMA patients (19%) likely because we included TMA without the typical features of TTP or HUS, which seem to be a frequent presentation of cancer-related TMA.[3] Overall, our results suggest that TMA is not uncommon in cancer patients and that, conversely, patients presenting with atypical features of TMA should be screened for cancers.[13] Indeed in 25% of our cancer patients, malignancy and TMA were first documented during the same admission, and Lechner and Obermeier had already reported in their series of 168 cancer-related TMA that in most cases TMA and cancer were simultaneously diagnosed.[3]

Our results should mitigate to belief that TMA develops almost exclusively in patients with metastatic solid tumors: whereas in the largest series published so far (168 aggregated cases of cancer-related TMA) approximately 90% of patients had solid tumors and 90% of them metastases,[3] only two-thirds of our patients had solid cancers (vs. a third of hematological malignancies) and about half of them with metastases. This discrepancy could be due to publication bias, as authors tend to report the most severe cases. Perhaps as a consequence, the mortality observed in the present study was not as dire as in some case series: whereas Lechner and Obermeier reported a median survival time of 4 months even after cancer treatment, the survival probability at 1 year was above 50% in our population.

Cancer-related TMA patients were different from TMA patients without malignancy in our study: more often men, older, and with more noncancer-related comorbidities. The prevalence of clinical diagnoses traditionally complicating TMA, like acute kidney injury or neurological complications, was not different between the two groups though. Lechner and Obermeier reported a high prevalence (about a third of patients) of respiratory complications and DIC in cancer patients developing TMA, much higher than traditionally observed in noncancer-related TMA. We likewise observed that DIC was more frequent in the subset of TMA patients with cancer but the incidence of acute respiratory failure was similar between the two groups. The prevalence of these complications was also much lower in our population (18% for acute respiratory failure and 5% for DIC); the fact that we used coding data whereas Lechner and Obermeier gathered comprehensive descriptions of clinical cases may account for this discrepancy.

Our study offers an insight into the variety of malignancies associated with TMA: hematological malignancies accounted for a third of the cases and, whereas non-Hodgkin lymphoma was the most frequent as previously reported,[3] almost all types of hematological malignancies were represented in our population. Regarding solid tumors, again a wide spectrum of cancers were represented; breast and lung cancers were the most frequent as previously reported,[3] but as compared with the series by Lechner and Obermeier we observed more pancreatic and less gastric and prostate cancers. Of note, a significant proportion of our patients had cancers with unknown primary, which was also the fifth most frequent type in Lechner and Obermeier's study after stomach, breast, prostate, and lung.[3]

Even though the prognosis of cancer-related TMA in our population was not as dismal as previously reported,[2,3] mortality remained high; hospital mortality was 6% in noncancer TMA patients, which is consistent with the most recent clinical trials in TTP for instance.[14] By contrast, cancer patients had a hospital mortality of approximately 17%, and malignancy was an independent risk factor for mortality in TMA patients overall. Hospital mortality even reached 30% in HSCT recipients, which is consistent with a recent study showing that TMA developed in approximately 10% of allogeneic HSCT recipients and was an independent predictor of mortality with a relative risk of 3.27.[15] In our series, the main predictors for hospital mortality in cancer-associated TMA were sepsis and mechanical ventilation, two factors traditionally associated with outcome in critically ill patients with cancers.[16,17] Interestingly, TPE was associated with decreased mortality in multivariate analysis both in the whole population and in the subset of patients with cancer. This result was expected in the whole population as TPE has been shown to improve survival in TTP[6]; however, its potential impact in cancer patients is more surprising as cancer-related TMA have been reported to not respond to TPE[13,18] which is not recommended in this setting.[13,19–21] Response to plasma therapy in cases of prostate cancer has been described though[3] and TPE is still being used despite the lack of evidence,[13,20,22] for lack of better treatment options. In our population, TPE may have been used in selected patients who seemed to have a better prognosis, and the resulting selection bias may account for our results.

Several study limitations deserve to be discussed: first, the MarketScan database mostly includes patients working for large employers and does not include patients on Medicare (above 65 years). A median age of 50 to 55 years has been reported for some cancer-related TMA,[3,23] but cases have been reported in patients aged 70 and older[3,23]; age also affects the incidence of specific types of cancer[24] and negatively impacts survival in patients with TTP,[25] so that our results may not be generalizable to patients above the age of 65. Second, we used the codes included in the database to define diagnoses of cancer and TMA as well as procedures and complications; the MarketScan database has been used for over 900 publications[26] over the past 20 years but our results obviously depend on the reliability of the coding data. Third, the lack of laboratory data did not allow us to definitely characterize TMA (TTP vs. HUS); a specific ICD-9 code exists for HUS and in the absence of a specific code for TTP we used as a surrogate the ICD-9 code of TMA combined with a procedure code for TPE, as previously used in other studies[11]; however, we cannot rule out a classification bias. Finally, the lack of data on cancer treatments received did not allow us to determine the mechanisms of TMA (direct consequence of the disease vs. complication of the chemotherapy or targeted therapy). These limitations being acknowledged, our study provides data on characteristics and outcomes in the largest series of cancer-related TMA reported so far.

In summary, in a large U.S. database, 20% of patients admitted for TMA had cancer, two-thirds of them solid tumors and one-third hematological malignancies. Cancer patients were older, more frequently male, and had more comorbidities than TMA patients without cancer. Hospital mortality was 17% for TMA patients with cancer versus 6% for patients without cancer, and malignancy was an independent risk factor for mortality.

What is known about this topic?

- Thrombotic microangiopathy has been associated with cancer in case series.
- Metastatic solid tumors have been most frequently involved.
- The prognosis is poor with short median survival and lack of response to therapeutic plasma exchange.

What does this paper add?

- In a large U.S. database, 20% of patients with thrombotic microangiopathy had cancer.
- Two-thirds of cancer patients had solid tumors (mostly pancreas, lung, breast, colorectal, and hepatobiliary, half of them metastatic) and one-third had hematological malignancies (lymphoma, acute leukemia, and multiple myeloma).
- In patients with thrombotic microangiopathy, hospital mortality was 16.6% for patients with cancer and 6.1% for those without cancer ($p < 0.001$). Malignancy was an independent risk factor for mortality.

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Conflict of Interest
None declared.

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