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Neoplastic and Non-Neoplastic Complications of Solid Organ Transplantation in Patients with Preexisting Monoclonal Gammopathy of Undetermined Significance (MGUS)

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ABBREVIATIONS

Healthcare Cost and Utilization Project (HCUP)

Interquartile range (IQR)

Monoclonal gammopathy of undetermined significance (MGUS)

Organ Procurement and Transplantation Network (OPTN)

Plasma cell myeloma (PCM)

Post-transplant lymphoproliferative disorder (PTLD)

Skeletal-related events (SRE)

Venous thromboembolism (VTE)

KEYWORDS
Monoclonal gammopathy of undetermined significance (MGUS)
Solid organ transplantation
Plasma cell myeloma
Multiple myeloma
Post-transplant lymphoproliferative disorder (PTLD)
Venous thromboembolism
Healthcare Cost and Utilization Project (HCUP)

ABSTRACT

Monoclonal gammopathy of undetermined significance (MGUS) occurs in 3-7% of the elderly population, with higher prevalence in renal failure patients, and is associated with a 25-fold increased lifetime risk for plasma cell myeloma (PCM), also known as multiple myeloma. Using the California State Inpatient, Emergency Department, and Ambulatory Surgery Databases components of the Healthcare Cost and Utilization Project (HCUP), we sought to determine if patients with MGUS who undergo solid organ allograft (n=22,062) are at increased adjusted relative risk (aRR) for hematological malignancy and other complications. Among solid organ transplant patients, patients with preexisting MGUS had higher aRR of PCM (aRR 19.46; 95%CI 7.05, 53.73; p<0.001), venous thromboembolic events (aRR 1.66; 95%CI 1.15, 2.41; p=0.007), and infection (aRR 1.24; 95%CI 1.06, 1.45; p=0.007). However, when comparing MGUS patients with and without solid organ transplant, there was decreased aRR for PCM with transplant (aRR 0.34; 95%CI 0.13, 0.88; p=0.027), and increased venous thromboembolic events (aRR 2.33; 95%CI 1.58, 3.44; p<0.001) and infectious risks, (aRR 1.44; 95%CI 1.23, 1.70;

p<0.001). While MGUS increased the risk of PCM overall following solid organ transplantation, there was lower risk of PCM development compared to MGUS patients who did not receive a transplant. MGUS should not preclude solid organ transplant.INTRODUCTION

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic precancerous condition that can progress to plasma cell myeloma (PCM), also known as multiple myeloma, or other hematologic malignancy. MGUS affects approximately 3% of people older than 50 years and 5% of those over 70 years of age [1]. This disorder is defined by the presence of a serum monoclonal protein at a concentration < 3 g/dL, a bone marrow examination with < 10% clonal plasma cells (if performed), and the absence of end-organ damage (anemia, hypercalcemia, lytic bone lesions, renal insufficiency and hyperviscosity) related to the monoclonal protein. Recent studies have shown that PCM is almost always preceded by a plasma cell disorder, most commonly MGUS [2], and the rate of progression from MGUS to PCM in the general population is predicted to be roughly 1% per year [3]. MGUS also increases the risk of developing PCM approximately 25-fold [4]. In addition, MGUS has been shown to increase the risk of other complications, including infection, venous thromboembolism (VTE), and skeletal-related events (SRE) such as osteoporosis and fracture [5-14].

Long term data regarding patients affected by preexisting MGUS who undergo solid organ transplant are scarce. Solid organ transplant requires long-term use of immunosuppression post-engraftment, which is associated with many risks overlapping those described above, including hematologic malignancies and post-transplant lymphoproliferative disease (PTLD), opportunistic infections, SRE and VTE. MGUS-affected patients usually are not excluded from transplantation; however, data on long-term outcomes are lacking and limited to single institution studies with relatively small patient numbers [15-17]. We hypothesized that patients with the precancerous condition, MGUS, are at heightened risk for these post-transplant complications.

METHODS

We utilized the 2005-2011 California State Inpatient Database (SID), State Emergency Department Database (SEDD), and State Ambulatory Surgery Database (SASD). These databases are part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Department of Health and Human Services, Agency for Healthcare Research and Quality. These databases include data from patients discharged from all non-federally funded community

hospitals in California, including both not-for-profit and investor-owned hospitals, as well as hospitals run by the state and local governments. Federally-run hospitals such as those run by Veterans Affairs or the Indian Health Service are not included, none of which are transplant centers in California. The California HCUP databases include a synthetic patient identifier that can be used to track individuals' utilization of care over the study period and across the emergency department, inpatient hospital, and ambulatory surgery settings. The SID includes over 100 variables including principal and secondary diagnoses and procedures, admission and discharge status, patient demographics characteristics (e.g., sex, age, and race), expected payment source, total charges, length of stay, and hospital characteristics (e.g. location, teaching status, and bed size). A complete list of variables is available in the SID data documentation online [18]. This study was reviewed and approved by the Institutional Review Board (IRB protocol #EM-14-30).

The study population includes patients undergoing solid organ transplant as defined by ICD-9-CM procedure codes (Supplemental Table). The main exposure of interest was MGUS, defined using ICD-9-CM diagnosis code 273.1. We searched patient records with diagnosis codes indicating MGUS on the same day or prior to solid organ transplant surgery. The primary outcomes of interest were morbidity and complications as defined by ICD-9-CM diagnosis codes in patient records after solid organ allograft. The outcomes of major interest were PCM, lymphoma, PTLD, opportunistic infection, VTE, and SRE. Infections included bacteremia, viremia, urinary tract infection, *Clostridium difficile*-associated diarrhea, endocarditis, pneumonia, influenza, and osteomyelitis. As a secondary analysis, we sought to investigate the association of solid organ transplant and poor outcomes among people that had MGUS. Here, the study population included any person with a diagnosis code of MGUS during the study period. The main effect was solid organ transplant occurring on the same date or after the first diagnosis of MGUS.

We conducted a descriptive analysis for all variables in our study. Comparisons between affected and non-affected subjects, MGUS(+) and MGUS(-), respectively, were made using Fisher's exact test for categorical variables, and Student's t-test for continuous variables. To protect patient confidentiality, the data use agreement from HCUP required that cells with nonzero counts less than 11 cannot be reported. Therefore, in some cases, we report the data as "≤10," rather than provide the exact cell count.

We used modified Poisson regression to model complications in MGUS(+) versus MGUS(-) transplant patients to produce risk ratios with robust confidence intervals [19]. To adjust for patient demographics, insurance status, and comorbidities we included a propensity score as a covariate in the Poisson regression models [20]. The propensity score is defined as the predicted probability of having MGUS conditional on each patient's baseline characteristics [21]. We calculated the propensity score using logistic regression with MGUS as the outcome and patient age, race, sex, count of all Elixhauser comorbidities, insurance, and year of transplant as the covariates. The Elixhauser comorbidity measure includes 30 comorbid conditions defined through secondary ICD-9-CM codes [22]. We also included specific comorbid conditions in the propensity score model if the frequency was greater than five cases in each group. The conditions included were hypertension, diabetes, hypothyroidism, anemia deficiency, electrolyte disorders, renal failure, and liver disease. Models were not fit for PTLD and lymphoma as no patients in the MGUS+ group experienced these outcomes. All of the above analysis was repeated in the MGUS population comparing solid organ transplant (+) vs solid organ transplant (-). All analyses were conducted on SAS version 9.3 for Unix (SAS Institute, Cary, NC).

RESULTS

Of the 24,358,669 patients in the California State Inpatient, Emergency, and Ambulatory Database from 2005-2011, we identified 22,062 solid organ transplant patients. Of these patients, 72 were found to be MGUS(+) prior to solid organ transplant. MGUS was not documented in the remaining 21,990 transplant patients prior to solid organ transplant. Demographic characteristics of solid organ transplant patients are shown in Table 1. Median age for the MGUS(+) group was somewhat older (61.5 years, versus 51 years for the MGUS (-) group, $p<0.001$). MGUS(+) solid organ transplant patients had significantly fewer comorbidities than MGUS(-) patients. As there were a number of demographic differences between the groups, propensity score adjusted risk ratios were utilized for further analysis.

Table 2 shows the outcomes of interest for solid organ transplant recipients according to MGUS status. There were ≤10 cases of PCM reported in the MGUS(+) group and 37 in the MGUS(-) group. Among solid organ transplant patients, those MGUS(+) patients had a nearly 20-fold higher risk of developing PCM compared to MGUS(-) (Table 3), with a propensity score adjusted risk ratio of 19.46 (95%CI 7.05, 53.73). While there were no cases of PTLD or

lymphoma in the MGUS(+) group, there were 161 and 193 cases, respectively, in the MGUS(-) group.

For the 72 patients in the MGUS(+) group, we identified a significantly higher incidence of several complications compared to the MGUS(-) group. Pulmonary embolism, VTEs, SREs, bacteremia, urinary tract infection, *Clostridium difficile* infection, and pneumonia were found to occur more frequently in the MGUS(+) group when compared to the MGUS(-) group (Table 2). Among solid organ transplant patients, MGUS(+) patients had a higher risk of developing VTE, SRE, and infection compared to MGUS(-) patients, with propensity adjusted risk ratios of 1.66 (95%CI 1.15, 2.41), 1.56 (95%CI 1.03, 2.37), and 1.24 (95%CI 1.06, 1.45), respectively (Table 3). In-hospital death risk was significantly increased for MGUS(+) solid organ transplant patients, compared to those unaffected by MGUS, with a propensity score adjusted relative risk of 1.58 (95% CI 1.18, 2.11).

While risk for complications or in-hospital death seemed higher for MGUS(+) solid organ transplant recipients, these data did not address the risk for similar MGUS(+) patients without transplant. First, we sought to determine the risk for these outcomes amongst all MGUS(+) patients with and without solid organ transplant. Utilizing propensity-score adjustment, we next sought to determine the risk for these outcomes in MGUS(+) patients according to transplant status. Amongst MGUS(+) patients, there were ≤ 10 cases of PCM in those receiving solid organ transplant, versus 1,631 for those without transplant (Table 4). In fact, PCM risk was decreased with solid organ transplant, with a propensity-adjusted risk ratio of 0.34 (95%CI 0.13, 0.88) for progression of MGUS to PCM. There were no reported PTLD or lymphoma cases in the transplanted MGUS(+) patients, although sample size was somewhat small. There were increased infectious and VTE events in the transplant group, with propensity score adjusted risk ratios of 1.44 (95%CI 1.23, 1.70) and 2.33 (95%CI 1.58, 3.44), respectively (Tables 4-5). SRE risk was not significantly different once adjusted for propensity score. Unadjusted in-hospital deaths were not significantly different for MGUS(+) patients with solid organ transplants, although significance was uncovered once the cohort was adjusted by propensity score, with an adjusted risk ratio of 1.47 (95% CI 1.09, 1.98) for those MGUS patients with an allograft.

DISCUSSION

Solid organ transplant recipients require long-term immunosuppression post-transplant that may lead to significant complications. We undertook this analysis of HCUP component databases to ascertain whether solid organ transplant recipients affected by a common disorder, MGUS, would be at heightened risk for serious complications that are shared by patients undergoing transplant immunosuppression and by patients with MGUS. Unlike the National Inpatient Sample, the California SID has the advantage of capturing data for a given patient at every California hospital, rather than just the data captured and submitted by the transplant center to the Organ Procurement and Transplantation Network (OPTN), and additionally contains diagnoses and procedures that are unavailable to the OPTN-based sources [23]. While those patients with preexisting MGUS experienced greater overall risks after solid organ transplant, the degree of increased risk suggests that these patients should not be excluded from solid organ transplant options.

Overall PTLD risk for solid organ transplant patients varies by organ-type and immunosuppression protocol. The risk is typically cited to be about 0.4% at one year for kidney transplant patients [24], but does not appear to be of high concern in this particular cohort of patients, with PTLD found in only 0.7% of the MGUS(-) patients and none of the MGUS(+) patients. On the other hand, compared to solid organ transplant patients without preexisting MGUS, our data demonstrated that solid organ transplant patients with preexisting MGUS had a significantly higher risk of VTE, SRE, and a variety of infections, including bacteremias, urinary tract infections, *Clostridium difficile*-associated diarrhea, and infectious pneumonia.

Consistent with other patient populations, we report that solid organ transplant patients with preexisting MGUS are also more likely to develop PCM than those without preexisting MGUS; however, this risk is similar to—or perhaps even lower than—that historically attributed to MGUS in patients who have not undergone transplant. Literature addressing PCM in MGUS patients following solid organ transplant is scarce and conflicting. Safadi et al [25] reported 4 of 7 multiple myeloma patients with kidney transplants demonstrated pre-existing MGUS. In a retrospective review of 1,593 solid organ transplant patients, Jimenez-Zipeda et al [26] reported that none of 34 patients with preexisting MGUS had progression to PCM, amyloid, or lymphoma, and they noted no association between preexisting MGUS and PTLD. In a slightly larger retrospective review of 3,518 kidney transplant patients that included 23 patients with preexisting MGUS, 4 (17.4%) patients developed a hematologic malignancy (2 smoldering PCM

and 2 PTLD) [17]. Another small case series in which 5 transplant patients with preexisting MGUS were followed showed 2 patients developed smoldering PCM after transplant [27], with other small studies reporting similar findings [15, 28]. In contrast, we found a somewhat reduced risk for PCM for patients with preexisting MGUS and solid organ transplant. Previous studies tended to be single center and often included patients who developed MGUS post-transplant. Interestingly, in a study of US veterans, MGUS patients with immune-mediated conditions, including autoimmunity, inflammatory disorders, and certain infectious disorders, were found to have increased risk of MGUS progression to PCM [29]. It is certainly possible that solid-organ transplant-related immunosuppression alters the likelihood of MGUS progression to PCM.

This study has limitations. There are inherent shortcomings in large retrospective database studies, including inconsistencies in-patient follow up, reporting, and coding practices. As the databases relied upon hospitalization or admission to an ambulatory surgery facility or emergency department for entry, subjects receiving care outside of these settings are not represented. Use of other large observational databases, however, suggests that many of the observations are consistent with randomized clinical trials and expert opinion [30-31]. In addition, as MGUS is present in about 3% of people greater than age 50 years [1], it is almost certainly underrepresented in this database. Outcomes of MGUS are variable, and a risk stratification system has been developed to predict the risk of progression from MGUS to PCM based on the amount of monoclonal protein, immunoglobulin type, and the serum free light chain ratio [32]. Unfortunately, these databases lack the data granularity to stratify patients based on such differentiation. Similarly, while diagnostic criteria for monoclonal gammopathy of renal significance has been proposed in 2012 [33], the date range from the database we utilized was prior to this proposed term and, in addition, that diagnostic terminology does not have an ICD-9 code independent from the MGUS code [34-35]. Similarly, the database does not include information on induction and maintenance immunosuppression use, which given the variability in practice and potential modifications in MGUS patients, could impact outcomes. Furthermore, despite the large sample size, the number of transplanted patients with MGUS and event rates were relatively low, thereby limiting statistical power. Sample size also prevented meaningful analysis of organ-specific outcomes—which is pertinent for kidney transplantation, as MGUS is more common in this population. While we adjusted by propensity score to accommodate

different levels of comorbidity to minimize selection bias, we can only control for known confounders that we could measure in our data. Further, the small number of cases in the MGUS group prevented us from direct adjustment of particular comorbidities, which may better control for patient differences. Finally, meaningful post-transplant survival analysis is not feasible with this dataset, as in-hospital mortality is biased towards patients requiring more frequent admission.

In conclusion, patients with preexisting MGUS who undergo solid organ transplantation have higher risks compared to MGUS-unaffected patients for developing complications such as PCM, VTE, SRE, and opportunistic infections. However, solid organ transplant in patients with preexisting MGUS does not appear to further increase the risk of progression to PCM in patients with solid organ transplant, nor do PTLD and lymphoma risks seem to increase. In contrast, solid organ transplant patients with preexisting MGUS are at higher risk for VTE, SRE, and infection, suggesting that closer monitoring for such events is warranted. While MGUS is a risk factor for future PCM, it should not preclude solid organ transplantation.

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Table 1: Characteristics of Solid Organ Transplant Patients.

	MGUS (+) N=72	MGUS (-) N=21,990	p
Age, years			
Median (IQR)	61.5 (52 – 66.5)	51 (37 – 60)	
Mean (std dev)	58.5 (11.6)	47.1 (17.3)	<0.001
Sex			0.549
Male	41 (56.9%)	13,390 (60.9%)	
Female	30 (41.7%)	8,493 (38.6%)	
Race			0.009
Black/Other	14 (19.4%)	5,265 (23.9%)	
Hispanic	13 (18.1%)	6,480 (29.5%)	
White	39 (54.2%)	9,535 (43.4%)	
Insurance			0.495
Private	31 (43.1%)	8,241 (37.5%)	
Public	40 (55.6%)	13,089 (59.5%)	
Comorbidities			<0.001
None	15 (20.8%)	2,960 (13.5%)	
1 to 2	19 (26.4%)	9,899 (45.0%)	
3 to 4	20 (27.7%)	6,377 (29.0%)	
Five or more	18 (25.0%)	2,754 (12.5%)	
Transplant type*			0.228
Kidney	45 (61.6%)	14,031 (63.8%)	
Liver	13 (17.8%)	5,064 (23.0%)	

Lung	≤10*	1,275 (5.8%)
Heart/lung	≤10*	64 (0.3%)
Heart	13 (17.8%)	1,866 (8.5%)

Of the 22,062 solid organ transplant patients identified in the database, 108 patients had missing sex data and 716 patients had missing race data. *Frequencies ≤10 are reported as such per the data use agreement.

Table 2: **Outcomes in Solid Organ Transplant Patients**

Outcome	MGUS (+) N=72	MGUS (–) N=21,990	p
PTLD	0	161 (0.7%)	0.999
PCM	≤10*	37 (0.2%)	<0.001
Lymphoma	0	193(0.9%)	0.999
VTE	20 (27.7%)	3,202 (14.6%)	0.004
Pulmonary embolism	≤10*	624 (2.8%)	0.017
Venous embolism/thrombosis	16 (22.2%)	2,920 (13.3%)	0.035
SRE	18 (25%)	2,320 (10.5%)	<0.001
Infection	50 (69.4%)	11,612 (52.8%)	0.006
Bacteremia	15 (20.8%)	2,029 (9.2%)	0.003
Viremia	≤10*	335 (1.5%)	0.999
Urinary tract infection	36 (50%)	7,076 (32.2%)	0.002
***C. difficile*-associated diarrhea**	15 (20.8%)	1,942 (8.8%)	0.001
Endocarditis	0	356 (1.6%)	0.634
Pneumonia	30 (41.7%)	6,159 (28.1%)	0.012

Influenza	0	516 (2.4%)	0.419
Osteomylitis	≤10*	650 (2.9%)	0.999
In-hospital death	29 (40.3%)	4,449 (20.2%)	<0.001

*Frequencies ≤10 are reported as such per the data use agreement.

Table 3: Outcomes in Solid Organ Transplant Patients

Outcome	Unadjusted Risk Ratio (95% CI)	p	Propensity score adjusted Risk Ratio (95% CI)	p
PCM	31.11 (12.62, 76.71)	<0.001	19.46 (7.05, 53.73)	<0.001
VTE	1.80 (1.24, 2.60)	0.002	1.66 (1.15, 2.41)	0.007
SRE	2.23 (1.50, 3.33)	<0.001	1.56 (1.03, 2.37)	0.036
Infection	1.24 (1.06, 1.44)	0.006	1.24 (1.06, 1.45)	0.007
In-hospital death	1.88 (1.42, 2.49)	<0.001	1.58 (1.18, 2.11)	0.002

R

isk ratio (RR) represents the increased risk of each outcome among those with MGUS compared to those without MGUS among solid organ transplant patients. Risk ratio for PTLD and Lymphoma were incalculable due to zero instances in the MGUS(+) group. The risk ratio and 95% confidence interval was obtained from modified Poisson regression models.

Table 4: **Outcomes in MGUS Patients**

Outcome	Transplant Recipients N=72	Non-transplant Patients N=12,060	p-value
PTLD	0	n/a	n/a
PCM	≤10*	1,631 (13.5%)	0.055

Lymphoma	0	591(4.9%)	0.051
VTE	20 (27.7%)	1,257 (10.4%)	<0.001
Pulmonary embolism	≤10*	444 (3.7%)	0.050
Venous embolism/thrombosis	16 (22.2%)	1,035 (8.6%)	<0.001
SRE	18 (25%)	3,530 (29.2%)	0.516
Infection	50 (69.4%)	6,806 (56.4%)	0.031
Bacteremia	15 (20.8%)	534 (4.4%)	<0.001
Viremia	≤10*	≤10*	0.052
Urinary tract infection	36 (50%)	4,347 (36.0%)	0.019
Clostridium difficile	15 (20.8%)	852 (7.1%)	<0.001
Endocarditis	0	204(1.7%)	0.636
Pneumonia	30 (41.7%)	4,184 (34.7%)	0.217
Influenza	0	99 (0.8%)	0.999
Osteomylitis	≤10*	383 (3.2%)	0.999
In-hospital death	29	3,942	0.207

*Frequencies ≤10 are reported as such per the data use agreement.

Table 5: Risk of outcomes among MGUS patients by transplant status

Outcome	Unadjusted Risk Ratio (95% CI)	p	Propensity score adjusted Risk Ratio (95% CI)	p
PCM	0.41 (0.16, 1.06)	0.067	0.34 (0.13, 0.88)	0.027
VTE	2.66 (1.83, 3.88)	<0.001	2.33 (1.58, 3.44)	<0.001
SRE	0.85 (0.57, 1.28)	0.441	1.33 (0.87, 2.03)	0.195
Infection	1.23 (1.05, 1.44)	0.008	1.44 (1.23, 1.70)	<0.001
In-hospital death	1.23 (0.93, 1.63)	0.147	1.47 (1.09, 1.98)	0.011

Risk ratio (RR) represents the increased risk of each outcome among those patients with MGUS comparing those with versus without solid organ transplant. Risk ratio for PTLD and Lymphoma were incalculable due to zero instances in the MGUS(+) group. The risk ratio and 95% confidence interval was obtained from modified Poisson regression models.

Supplemental Table: ICD-9 Diagnosis and Procedure Codes

ICD-9 Diagnosis and Procedure Codes	
Diagnosis	**Code**
Monoclonal paraproteinemia (MGUS)	273.1
Multiple myeloma (or PCM)	203
PTLD	238.77
Lymphoma	200, 201, 202
Venous thromboembolism (VTE)	
Pulmonary embolism	415.1, 416.2
Venous embolism and thrombosis	453
Skeletal related events (SRE)	
Osteoporosis, pathologic fracture	733.0-733.1
Infections	
Viremia	790.8
Bacteremia	790.7
Endocarditis	421, 424.9
Urinary tract infection	599.0
Clostridium difficile	008.45
Pneumonia	480-486
Influenza	487-488
Osteomyelitis	730
Solid organ transplant	
Kidney	55.6

Liver	50.5
Lung	33.5
Heart/lung	33.6
Heart	37.51
Pancreas	52.8