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Delayed-onset cytomegalovirus disease coded during hospital readmission after kidney transplantation¹

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Abstract

Background—Use of prophylactic anti-CMV therapy for 3 to 6 months after kidney transplantation can result in delayed-onset CMV disease. We hypothesized that delayed-onset CMV disease (occurring 100 days post-transplant) occurs more commonly than early-onset CMV disease, and that it is associated with death.

Methods—We assembled a retrospective cohort of 15,848 adult kidney transplant recipients using 2004 to 2010 administrative data from the California and Florida Healthcare Cost and Utilization Project State Inpatient Databases. We identified demographic data, comorbidities, CMV disease coded during readmission and inpatient death. We used multivariate Cox proportional hazards modeling to determine risk factors for delayed-onset CMV disease and inpatient death.

Results—Delayed-onset CMV disease was identified in 4.0% and early-onset CMV disease was identified in 1.2% of the kidney transplant recipients. Risk factors for delayed-onset CMV disease included previous transplant failure or rejection (HR 1.4) and residence in the lowest-income ZIP codes (HR 1.2). Inpatient death was associated with CMV disease occurring 101–365 days post-transplant (HR 1.5), CMV disease occurring > 365 days post-transplant (HR 2.1), increasing age (by decade: HR 1.5), non-white race (HR 1.2), residence in the lowest-income ZIP codes (HR

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1.2), transplant failure or rejection (HR 3.2), prior solid organ transplant (HR 1.7) and several comorbidities.

Conclusions—These data showed that delayed-onset CMV disease occurred more commonly than early-onset CMV disease, and that transplant failure or rejection is a risk factor for delayed-onset CMV disease. Further research should be done to determine if delayed-onset CMV disease is independently associated with death.

Keywords

cytomegalovirus; kidney transplantation; administrative data

INTRODUCTION

Kidney transplant recipients require immunosuppressive medications to prevent allograft rejection which markedly increases their risk of developing cytomegalovirus (CMV) disease (1–3), which can manifest as CMV syndrome, or tissue-invasive CMV disease with hepatitis, enteritis, colitis, pneumonitis, nephritis and rarely retinitis (3–9). Significant research has been devoted to the prevention of CMV disease after kidney transplantation, and CMV-seronegative recipients of organs from CMV-seropositive donors (D+/R–), as well as CMV-seropositive transplant recipients (R+) in the United States now generally receive prophylactic anti-CMV therapy for at least 3 months post-transplant (3;10–14). This however has led to the emergence of delayed-onset CMV disease, typically categorized as either late-onset CMV disease (occurring between discontinuation of anti-CMV prophylaxis and 1 year post-transplant) (13;15–19), or very late-onset CMV disease (occurring more than 1 year post-transplant) (19–21).

Delayed-onset CMV disease has not been well studied, given difficulties in assembling representative study cohorts, and the propensity for up to one-third of transplant recipients to transition their care away from transplant centers to non-transplant centers nearer their homes post-transplant (22), which limits long-term follow-up. The incidence of late-onset CMV disease among D+/R– kidney transplant recipients has been reported in single-center studies to be 19% to 48%, and generally occurs 2 to 3 months after the cessation of anti-CMV prophylaxis (16–18;23;24). One study reported that late-onset CMV disease was associated with an almost 3-fold increased risk of allograft loss or death (16), while another study did not demonstrate an association with death or graft loss (18). Very late-onset CMV disease is even less well-characterized, but has been reported to present atypically (20), and has been associated with an increased risk of death compared to late-onset CMV disease in a small case-control study (21).

To expand our understanding of the scope, risk factors and outcomes associated with delayed-onset CMV disease among kidney transplant recipients, we assembled a large cohort of kidney transplant patients using the Agency for Healthcare Research and Quality – Healthcare Cost and Utilization Project (AHRQ-HCUP) – State Inpatient Databases (SID) of California and Florida. The SID are composed of demographic and billing data that capture diagnoses and procedures occurring during hospitalization through *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding. We

focused on examining the SID from California and Florida given the availability of patient-level encrypted identifiers to link admissions within and across hospitals over time and the states' population diversity. Assuming widespread use of prophylactic anti-CMV therapy for D+/R- and R+ patients for at least 3 months post-transplant, we hypothesized that delayed-onset CMV disease (> 100 days post-transplant) now occurs more commonly than early-onset CMV disease (< 100 days post-transplant), and that it is associated with death.

RESULTS

Our study population consisted of 15,848 adult kidney transplant recipients (Table 1). The median age was 51 and 40% were female. Fifty-eight per cent of patients were non-white, and 36% were Hispanic, Asian or Pacific Islander. The majority of kidney transplant recipients resided in large metropolitan areas, and had Medicare as their expected primary insurance payer. Patients who resided in ZIP codes with the lowest median incomes, or whose ZIP code category according to median income was missing, accounted for 34% of the study population. Approximately 4% of patients had a prior solid-organ transplant, and 2.5% had a prior kidney transplant. Thirty-seven percent of patients had pre-existing diabetes mellitus, and 13% had a Charlson comorbidity index > 4. The median duration of follow-up was 4 years (IQR 2.4–5.6 years).

New-onset CMV disease coded at hospital readmission occurred in 5.2% of kidney transplant recipients (Table 2). Coding for CMV disease likely represents microbiological or histopathologic evidence of CMV replication along with signs and symptoms consistent with CMV disease. Approximately 1.2% of transplant recipients had early-onset (< 100 days post-transplant), 2.5% had late-onset (101 to 365 days post-transplant) and 1.5% had very late-onset (> 365 days post-transplant) CMV disease. Among patients hospitalized with newly-coded CMV disease (first readmission), 26% were coded for esophagogastroduodenoscopy (EGD), flexible sigmoidoscopy or colonoscopy; 12% were coded for pneumonia or hepatitis; and 35% were coded with EGD, flexible sigmoidoscopy, colonoscopy, pneumonia or hepatitis, possibly reflecting tissue-invasive CMV disease. A greater proportion of hospitalizations coded with late and very late-onset CMV disease had codes indicating possible tissue-invasion, compared to hospitalizations coded with early-onset CMV disease. Approximately 55% were coded for transplant failure or rejection; 13% were coded for percutaneous kidney biopsy; and 11% were coded for hemodialysis.

Univariate and multivariate Cox proportional hazard ratios for risk factors associated with delayed-onset CMV disease coded during hospitalization are shown in Table 3. Previous transplant failure or rejection was significantly associated with a 43% increased risk of delayed-onset CMV disease. Previous transplant failure or rejection preceded delayed-onset CMV disease by a median of 7.2 months (IQR, 3.9–15.5 months). Residence in ZIP codes with the lowest median incomes, or with missing information, was significantly associated with a 19% increased risk of delayed-onset CMV disease. Diabetes mellitus was modestly associated with delayed-onset CMV disease on univariate analysis (HR 1.2), and approached statistical significance on multivariate analysis ($p=0.055$). Non-white race was significantly associated on multivariate analysis with a 19% decreased risk of delayed-onset CMV disease.

Ten per cent of patients with early-onset and 11% of patients with late-onset CMV disease died in-hospital, whereas 19% of patients with very late-onset CMV disease died in-hospital. The median time between coding for CMV disease and death for patients who had early and late-onset CMV disease was 315 days and 367 days respectively, while the median time between coding for CMV disease and death for patients who had very late-onset CMV disease was 72 days. In-hospital death occurred in 5.8% (919/15,848) of the study cohort, with 597 (3.8%) of the deaths occurring > 365 days post-transplant. On Kaplan-Meier analysis, patients with CMV disease coded during readmission had lower survival compared to patients with no coding for CMV disease (Figure 1). Approximately 5.4% of patients with no coding for CMV disease died (median time to death post-transplant, 724 days, IQR 169 to 1,330 days), whereas 13.2% of patients coded with CMV disease died (median time to death post-transplant 746 days, IQR 407 to 1,698 days).

Univariate and multivariate Cox proportional hazard ratios for risk factors associated with death are shown in Table 4. Late and very late-onset CMV disease were significantly associated on multivariate analysis with a 1.5 and 2.1-fold increased risk of death after transplantation respectively, whereas early-onset CMV disease was not. Other risk factors for inpatient death identified on multivariate analysis were increasing age (HR 1.5); non-white race (HR 1.2); residence in ZIP codes with the lowest median incomes, or with missing information (HR 1.2); transplant failure or rejection (HR 3.2); prior solid-organ transplant (HR 1.7); diabetes mellitus (HR 1.5); congestive heart failure (HR 1.5); coagulopathy (HR 1.3); peripheral vascular disease (HR 1.5); chronic pulmonary disease (HR 1.2); and pulmonary circulation disease (HR 1.5). CMV disease coded during readmission with no codes for possible tissue-invasion was associated with a 1.4-fold increased risk of death ($p=0.010$), whereas CMV disease coded during readmission with codes for possible tissue-invasion was associated with a 2.1-fold increased risk of death ($p<0.001$), adjusted for the same covariates.

DISCUSSION

We assembled a large cohort of adult kidney transplant patients who received transplants from 2004 to 2010 using inpatient hospital billing data from California and Florida and followed them over time to determine the incidence of CMV disease coded during hospital readmission. We hypothesized that late and very late-onset CMV disease occurred more commonly than early-onset CMV disease, and that delayed-onset CMV disease was associated with death. Analysis of these billing data with regards to kidney transplantation and CMV disease has never been done, and provides more generalizable information regarding the incidence, risk factors and outcomes associated with CMV disease coded during readmission.

We found that late and very late-onset CMV disease coded during readmission occurred more commonly than early-onset CMV disease. Notably, our study cohort was comprised of a subset of kidney transplant recipients in the United States, where anti-lymphocyte antibodies are used frequently for induction immunosuppressive therapy (16;23). Anti-lymphocyte antibodies are infrequently used as induction therapy in other countries (e.g., United Kingdom), due to concerns over its side effects (25). A study from the United

Kingdom reported the incidence of late-onset CMV disease among D+/R– kidney transplant recipients to be 19%, of which only 10% had tissue-invasive disease (24). In contrast, 2 studies from the U.S. reported the incidence of late-onset CMV disease among D+/R– kidney transplant patients to be 26% and 27%, of which 34% and 51% had tissue-invasion (16;23). Prophylactic anti-CMV therapy with ganciclovir or valganciclovir was used for at least 3 months in all 3 studies. Anti-lymphocyte antibodies were frequently used as induction therapy in the U.S. studies, whereas it was not used in the U.K. study. In our current study, 35% of cases of CMV disease coded during hospital readmission were assessed as having possible tissue-invasive CMV disease, consistent with the proportion in the U.S. studies. Interestingly, EGD, flexible sigmoidoscopy or colonoscopy were commonly performed during hospitalizations in which CMV disease was coded, indicating significant gastrointestinal symptomatology during the hospitalization. This is not unexpected, given that CMV disease among kidney transplant recipients commonly manifests as esophagitis, gastritis, enteritis or colitis (16;18;26). In contrast, other potential indicators of tissue invasion by CMV, such as codes for pneumonia and hepatitis, were found less commonly, possibly reflecting the relative infrequency of CMV pneumonitis and hepatitis in kidney transplant recipients (16;18). Indicators of allograft dysfunction, such as coding for transplant failure or rejection, performance of percutaneous kidney biopsy and hemodialysis frequently co-occurred with CMV disease coding, possibly reflecting a bi-directional relationship between CMV and kidney failure (27). CMV can cause nephritis (3;28), trigger upregulation of alloantigens thereby promoting allograft rejection (27), or cause gastrointestinal tract disease resulting in emesis and/or diarrhea and subsequent dehydration and acute tubular necrosis (16;18;26). Conversely, kidney failure can cause decreased clearance of immunosuppressive medications, or prompt the administration of anti-lymphocyte antibodies or high-dose steroids if acute allograft rejection is proven or suspected, thereby increasing the net state of immunosuppression and promoting CMV disease (15;27;29;30).

Factors associated with increased risk of delayed-onset CMV disease coded during readmission in this cohort were previous transplant failure or rejection and patient residence in ZIP codes with the lowest median incomes. The association between allograft rejection and the subsequent development of CMV disease is well-documented (8;15;31), and is presumably due to the administration of lymphocyte depleting therapy or high-dose steroids to treat acute cellular rejection (3;27;29;30). More recent studies however, do not describe an association between allograft rejection and subsequent CMV disease (18;19;23), and one in particular, found a seemingly protective effect of acute graft rejection against CMV disease (16). This change may be due to academic transplant centers restarting prophylactic anti-CMV therapy (valganciclovir, oral ganciclovir or intravenous ganciclovir) for 1 to 3 months, or instituting a pre-emptive anti-CMV strategy concurrent with treatment for acute allograft rejection, as recommended by the American Society of Transplantation (3). Our study shows that coding for transplant failure or rejection was associated with an increased risk for delayed-onset CMV disease, possibly indicating that medical providers do not always reinstitute prophylactic or preemptive strategies to prevent CMV disease upon commencing treatment for allograft rejection. Patient residence in the lowest-income ZIP codes was modestly associated with CMV disease. The mechanisms that link low

socioeconomic status to inferior transplant outcomes are likely multifactorial, and include contextual and individual-level factors (32;33). It is possible that the expense of preventive anti-CMV therapy leads to non-adherence in patients with lower socioeconomic status (34), or that access to outpatient continuity care is more difficult (32). Our current study relied on receipt of inpatient care, since the SID consist of billing data from hospitalizations. However, these hospital admissions may have resulted from impaired access to continuity outpatient care, leading to the development of CMV disease requiring hospitalization.

Diabetes mellitus was modestly associated with delayed-onset CMV disease coded during hospitalization on univariate analysis, and approached statistical significance on multivariate analysis. This is an observation that has not been previously demonstrated in other studies presumably because of lack of power (16;19;21). Patients with poorly-controlled diabetes mellitus are presumed to be immunocompromised because of multiple hyperglycemia-related immune system impairments (35–39), and most relevantly may have decreased production of interferon-gamma and tumor necrosis factor-alpha by T-cells (40), which may result in increased risk of CMV disease.

Non-white race appeared protective against delayed-onset CMV disease. Non-white persons have a CMV-seropositivity prevalence of approximately 75% compared to approximately 40% among whites, according to the National Health and Nutrition Examination Surveys (NHANES) from 1988 to 2004 (41). A consequence of this would be that white patients are more likely to be D+/R– compared to persons of other races, and therefore as a group would be more likely to develop CMV disease (3;8;27). It has been shown that failure to develop effective CMV-specific T-cell immunity predicts CMV disease (42), a condition presumably more likely to develop in CMV-naïve patients than those with immune memory.

We found that late and very late-onset CMV disease coded during readmission was associated with inpatient death, while early-onset CMV disease was not. The underlying reason for the association between late and very late-onset CMV disease and death is most likely the development of allograft failure. Acute cellular rejection necessitates the administration of anti-lymphocyte antibodies or high-dose steroids which markedly increases the risk of CMV disease (15;27;29;30). Acute cellular rejection may culminate in allograft failure and hemodialysis, which increase the risk of death (43;44). Delayed-onset CMV disease therefore, may merely reflect the occurrence of allograft failure, and it is likely that allograft failure, not CMV disease, is directly associated with death. We attempted to control for allograft failure using coding for prior transplant failure or rejection; however, residual confounding is likely present. In addition, delayed-onset CMV disease coded during hospitalization may represent a subset of cases with more tissue-invasive disease, compared to all cases of CMV disease that occur in kidney transplant recipients. In our study, we found that more than one-third of hospitalizations in which CMV disease was coded had evidence for possible tissue invasion by CMV, and that delayed-onset CMV disease had a greater frequency of these codes compared to early-onset CMV disease. We also found that tissue-invasive CMV disease had a greater association with death than CMV disease with no evidence for tissue invasion. It has been reported that delayed-onset CMV disease presents atypically (20) and may not be recognized until it has resulted in tissue-

invasion. It is possible that severe tissue-invasive CMV disease contributes to the causal pathway for death.

The strengths of our study are the size of the study population, the long duration of follow-up and the generalizability of its findings. However, it has several limitations. Administrative data based on ICD-9-CM codes recorded for medical billing may be inaccurate. There is only one procedure code for kidney transplantation, which precludes differentiation between cadaveric and living related donor transplantation. Only conditions coded during a hospitalization within the state can be identified using the SID. Conditions managed in the outpatient setting, and the site of outpatient follow-up cannot be captured, as are important risk factors for CMV disease such as donor and recipient CMV serostatus, induction and maintenance immunosuppressive therapy, and the choice, route and duration of anti-CMV therapy.

In summary, we have shown using a large cohort of adult kidney transplant recipients observed over an extended period of time that late and very late-onset CMV disease coded during readmission occurs more frequently than early-onset CMV disease, and that previous transplant failure or rejection is a risk factor for delayed-onset CMV disease. Future studies should focus on determining the accuracy of ICD-9-CM coding for CMV disease coded during hospitalization in both transplant centers and non-transplant centers, and determining whether severe tissue-invasive CMV disease is independently associated with death.

METHODS

Study design and patient population

We conducted a retrospective cohort study of patients ≥ 18 years of age who underwent kidney transplantation, identified using ICD-9-CM code 55.69. We included kidney transplant recipients from 2004 to 2010 in the California SID and 2006 to 2010 in the Florida SID (n=15,848). These years were used to accrue 1 year of preexisting data to determine comorbidities, and at least 1 year of follow-up data. We excluded patients coded for CMV disease in the year prior to transplantation, and during the transplant hospitalization (n=168) because we were interested only in new-onset CMV disease. In addition, we excluded patients who received another solid-organ transplant during the same hospital stay (n=1,019) and patients coded for kidney transplant at a pediatric hospital (n=46) or a hospital coding for less than 1 transplant per year (n<11). The American Hospital Association (AHA) Annual Hospital Survey was used to determine whether transplant centers were pediatric or non-pediatric hospitals. This study was considered exempt from Human Research Protection Office oversight by the Institutional Review Board of Washington University in St. Louis.

Demographic data, comorbidities and prior transplantation

We ascertained the demographic characteristics of our study cohort at the time of transplantation (age, sex, race, patient location, median income of patient ZIP code and expected primary insurance payer), history of prior solid-organ transplantation and comorbidities. We identified prior solid-organ transplantation using ICD-9-CM codes

V42.0, V42.7, V42.1, V42.6, V42.83 and V42.84 from 1 year before the transplant and through the transplant admission and using ICD-9-CM procedure codes 50.59, 37.51, 33.50 to 33.52, 33.6, 52.80 and 46.97 prior to the transplant admission. Comorbidities within 1 year before transplantation and during the transplant hospitalization were identified using the comorbidity software provided by HCUP (45). The Charlson comorbidity index was computed using software adapted from the Surveillance, Epidemiology and End Results (SEER) Program (46).

Follow-up

Subsequent inpatient admissions of the study cohort were identified from the SID using the encrypted patient-level identifier to link across admissions. Newly-coded CMV disease occurring after transplantation was identified using ICD9-CM diagnosis code 078.5, and was classified according to time of onset. Assuming that most transplant centers in the United States provide prophylactic anti-CMV therapy for at least 3 months after transplantation, early-onset CMV disease was defined as occurring at readmissions ≤ 100 days post-transplant, while delayed-onset CMV disease was defined as occurring > 100 days post-transplant. Delayed-onset CMV disease was further categorized into late-onset CMV disease (occurring 101 to 365 days post-transplant) and very late-onset CMV disease (occurring > 365 days post-transplant). New-onset transplant failure or rejection was identified using code 996.81 at readmission or during the transplant admission if the patient did not have a history of prior kidney transplantation. Repeat solid-organ transplantation on a subsequent admission was identified using ICD-9-CM procedure codes 55.69, 50.59, 37.51, 33.50 to 33.52, 33.6, 52.80 and 46.97. The hospitalization during which CMV disease was coded was further characterized by identifying codes for esophagogastroduodenoscopy (EGD), flexible sigmoidoscopy or colonoscopy (45.12, 45.13, 45.14, 45.16, 45.23, 45.24 and 45.25), which may have been used to diagnose gastrointestinal tract CMV disease; pneumonia (484.1); hepatitis (573.1); and percutaneous kidney biopsy (55.23) and hemodialysis (39.95), which indicate allograft dysfunction. Time to death (during an inpatient hospital stay) was determined using the discharge status variable.

Statistical analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the study cohort. Potential risk factors for delayed-onset CMV disease and inpatient death coded during hospitalization, including age, sex, race, patient location, median income of patient ZIP code, primary expected payer, previous transplant failure or rejection, prior solid-organ transplantation and selected comorbidities were analyzed using univariate and multivariate Cox proportional hazard modeling. Only patients who survived > 100 days post-transplant and were never coded with CMV disease ≤ 100 days post-transplant were included in the analysis for risk factors for delayed-onset CMV disease. The proportional hazards assumption was evaluated for each variable using visual inspection of log-log survival curves and the correlation between Schoenfeld residuals for a particular covariate and the ranking of individual failure times (47). Statistical significance was set at a p-value 0.05. All analyses were done using SAS version 9.2 (Cary, North Carolina).

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Abbreviations

CMV	cytomegalovirus
AHRQ-HCUP	Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project
SID	State Inpatient Databases
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
SEER	Surveillance, Epidemiology and End Results
AHA	American Hospital Association
EGD	esophagogastroduodenoscopy
IQR	interquartile range
HR	hazard ratio
NHANES	National Health and Nutrition Examination Surveys

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Figure 1.
Time (days) to inpatient death in a cohort of 15,848 adult kidney transplant recipients, stratified according presence or absence of CMV disease coded during hospitalization.

Table 1

Demographic and clinical characteristics of 15,848 kidney transplant recipients at the time of organ transplantation.

Variables	All recipients
Age, years	
Mean $\pm$ SD	50.28 $\pm$ 13.68
Median (interquartile range)	51 (41 – 61)
Female sex (%)	39.82
Race (%)	
White	42.31
Black	15.64
Hispanic	24.96
Asian or Pacific Islander	10.68
Other or missing	6.42
Patient location (urban-rural) (%) ¹	
Large metropolitan	72.60
Small metropolitan	23.31
Micropolitan	2.85
Not metropolitan or micropolitan	0.88
Missing	0.36
Median income of patient ZIP code (%) ²	
First quartile (poorest)	21.47
Second quartile	21.18
Third quartile	23.24
Fourth quartile (wealthiest)	21.31
Missing	12.79
Expected primary insurance payer (%)	
Medicare	
< 65 years of age	50.15
65 years of age	14.39
Private insurance	30.18
Medicaid, self-pay, no charge or other	5.28
Prior transplant (%)	3.98
Kidney	2.51
Liver	0.73
Heart	0.40
Lung	0.11
Pancreas	0.44
Heart-Lung	<0.01

Variables	All recipients
Intestine	<0.01
Comorbidities (%)	
Hypertension	95.85
Diabetes mellitus	37.21
Congestive heart failure	10.92
Hypothyroidism	9.42
Obesity	9.40
Coagulopathy	9.09
Peripheral vascular disease	8.99
Chronic pulmonary disease	8.11
Depression	7.43
Valvular disease	6.99
Neurologic disorders	5.64
Rheumatoid arthritis or collagen vascular disease	5.43
Liver disease	4.87
Pulmonary circulation disease	3.04
Psychoses	1.92
Drug abuse	1.89
Paralysis	1.12
Alcohol abuse	1.05
Solid tumor without metastasis	0.42
HIV	0.29
Lymphoma	0.16
Charlson comorbidity index (%)	
4	87.37
> 4	12.63
Duration of follow-up, years	
Mean	4.1
Median (interquartile range)	4 (2.4 – 5.6)

¹ Large metropolitan – at least 1 million residents; Small metropolitan – less than 1 million residents; Micropolitan – adjacent to large or small metropolitan area.

² Based on quartiles of the estimated median household income of the patient's ZIP code for the state. Values vary by year and state. According to the U.S. Census Bureau, in 2011: first quartile: <\$5,000-\$29,999; second quartile: \$30,000-\$54,999; third quartile: \$55,000-\$94,999; fourth quartile: >\$95,000.

Number of patients coded for new-onset CMV disease during hospitalization¹, coincident conditions and procedures, and subsequent inpatient death in a cohort of 15,848 kidney transplant recipients.

Table 2

	All CMV	Early	Late	Very late
Number of patients (%)	825 (5.21)	184 (1.16)	400 (2.52)	241 (1.52)
EGD, flexible sigmoidoscopy or colonoscopy	213 (25.82)	42 (22.83)	106 (26.50)	65 (26.97)
Pneumonia or hepatitis	99 (12.00)	11 (5.98)	54 (13.50)	34 (14.11)
Possible tissue-invasive CMV disease ²	288 (34.91)	50 (21.17)	143 (35.75)	95 (39.42)
Transplant failure or rejection	451 (54.67)	101 (54.89)	214 (53.50)	136 (56.43)
Percutaneous kidney biopsy	107 (12.97)	29 (15.76)	51 (12.75)	27 (11.20)
Hemodialysis	88 (10.67)	15 (8.15)	30 (7.50)	43 (17.84)
Died	109 (13.21)	18 (9.78)	45 (11.25)	46 (19.09)
Median time to death (interquartile range)	175 (33–642)	315 (31 – 1,212)	367 (46 – 1,075)	72 (33 – 234)

¹The first readmission coded for CMV disease was used for analysis.

²Coding for EGD, flexible sigmoidoscopy, colonoscopy, pneumonia or hepatitis.

Cox proportional hazard model for risk factors associated with delayed-onset CMV disease coded during hospitalization.

Table 3

Risk factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Increasing age at time of transplantation per decade	1.07 (1.01–1.13)	0.021	1.05 (0.99–1.12)	0.098
Female sex	1.02 (0.87–1.20)	0.805		
Non-white race	0.84 (0.72–0.98)	0.027	0.81 (0.69–0.95)	0.009
Patient location non-metropolitan	1.12 (0.76–1.66)	0.561		
Patient residence in lowest-income ZIP codes, or missing	1.18 (1.01–1.38)	0.042	1.19 (1.01–1.40)	0.036
Primary payer				
Private insurance or Medicare	65 years of age	1.00		
Medicare < 65 years of age, Medicaid, self-pay, no charge or other	1.07 (0.91–1.25)	0.403		
Previous transplant failure or rejection	1.44 (1.23–1.69)	<0.001	1.43 (1.22–1.68)	<0.001
Prior transplant				
Kidney	1.01 (0.68–1.50)	0.944		
Liver	0.98 (0.60–1.61)	0.934		
Heart	0.21 (0.03–1.50)	0.119		
Pancreas	2.53 (1.13–5.64)	0.024		
	1.44 (0.54–3.86)	0.462		
Diabetes mellitus	1.24 (1.06–1.45)	0.007	1.17 (1.00–1.38)	0.055
Charlson comorbidity index > 4	1.29 (1.04–1.61)	0.021		

Table 4

Cox proportional hazard model for risk factors associated with inpatient death.

		Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
New-onset CMV disease					
Early-onset (100 days post-transplant)		1.77 (1.11–2.83)	0.016	1.34 (0.84–2.15)	0.217
Late-onset (101 to 365 days post-transplant)		2.08 (1.54–2.82)	<0.001	1.47 (1.09–1.99)	0.012
Very late-onset (> 365 days post-transplant)		3.14 (2.34–4.23)	<0.001	2.08 (1.54–2.81)	<0.001
Increasing age at time of transplantation per decade		1.64 (1.56–1.74)	<0.001	1.54 (1.46–1.63)	<0.001
Female sex					
		0.83 (0.72–0.95)	0.007		
Non-white race					
		1.12 (0.98–1.28)	0.092	1.18 (1.03–1.35)	0.018
Patient location non-metropolitan					
		0.99 (0.70–1.41)	0.961		
Patient residence in lowest-income ZIP codes, or missing					
		1.21 (1.06–1.38)	0.006	1.15 (1.00–1.32)	0.049
Primary payer					
Private insurance or Medicare	65 years of age	1.00			
Medicare < 65 years of age, Medicaid, self-pay, no charge or other		0.97 (0.85–1.11)	0.674		
Transplant failure or rejection					
		3.77 (3.19–4.46)	<0.001	3.20 (2.70–3.79)	<0.001
Prior transplant					
Kidney		1.66 (1.27–2.16)	<0.001	1.66 (1.27–2.17)	<0.001
Liver		1.55 (1.11–2.16)	0.010		
Heart		2.02 (1.17–3.49)	0.012		
Lung		3.06 (1.64–5.71)	<0.001		
Pancreas		2.75 (0.89–8.55)	0.080		
		0.99 (0.37–2.64)	0.981		
Comorbidities					
Hypertension		0.98 (0.71–1.33)	0.874		
Diabetes mellitus		2.34 (2.05–2.66)	<0.001	1.48 (1.29–1.70)	<0.001
Congestive heart failure		2.55 (2.18–2.97)	<0.001	1.52 (1.29–1.79)	<0.001

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Hypothyroidism	1.38 (1.13–1.70)	0.002		
Obesity	1.36 (1.11–1.67)	0.003		
Coagulopathy	1.58 (1.30–1.93)	<0.001	1.30 (1.06–1.59)	0.011
Peripheral vascular disease	2.67 (2.27–3.14)	<0.001	1.51 (1.27–1.79)	<0.001
Chronic pulmonary disease	1.68 (1.38–2.04)	<0.001	1.24 (1.02–1.52)	0.035
Depression	1.25 (0.99–1.57)	0.057		
Valvular disease	1.96 (1.60–2.39)	<0.001	1.23 (0.99–1.53)	0.059
Neurologic disorders	1.05 (0.79–1.39)	0.752		
Rheumatoid arthritis or collagen vascular disease	0.77 (0.56–1.06)	0.113		
Liver disease	1.51 (1.17–1.95)	0.002		
Pulmonary circulation disease	2.71 (2.09–3.52)	<0.001	1.48 (1.12–1.96)	0.006
Psychoses	1.27 (0.82–1.96)	0.275		
Drug abuse	0.86 (0.51–1.46)	0.576		
Paralysis	0.98 (0.53–1.83)	0.956		
Alcohol abuse	1.70 (1.04–2.79)	0.035		
Solid tumor without metastasis	1.69 (0.76–3.78)	0.199		
HIV	1.29 (0.42–4.01)	0.658		
Lymphoma	1.53 (0.38–6.11)	0.546		
Charlson comorbidity index > 4	2.78 (2.40–3.23)	<0.001		