Clinical and Military Outcomes of Kidney Diseases Diagnosed in Active Duty Service Members

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ABSTRACT

Introduction:
Renal biopsy is a valuable tool for determining diagnosis, management, and prognosis of intrinsic kidney diseases. Indications for biopsy depend on the clinical presentation. Within the military, renal biopsies also enable medical review boards to make military service fitness assessments after diagnosis of a kidney disease. There are no recent studies evaluating kidney disease diagnoses and clinical outcomes after renal biopsy at military treatment facilities. Additionally, no studies have examined overall healthcare and military career outcomes following renal biopsy.

Materials and Methods:
We retrospectively reviewed all native renal biopsies performed on active duty beneficiaries at the Walter Reed National Military Medical Center from 2005 to 2020. We determined the prevalence of those who progressed to end-stage kidney disease (ESKD), kidney transplantation, doubling of serum creatinine, nephrotic-range proteinuria (NRP; proteinuria >3.5 g/day), medical evaluation board (MEB) outcomes, and death. The Armed Forces Health Longitudinal Technology Application and the Joint Legacy Viewer electronic medical record systems were used to access clinical and laboratory data at the time of biopsy and subsequent outcomes. Death data were collected using the Defense Suicide Prevention Office database.

Results:
There were 169 patients in the cohort, with a mean follow-up of 7.3 years. Mean age was 32 years; 79% male; 48% white; and 37% black. Sixty-seven percentage of them were junior or senior enlisted. The most common indication for renal biopsy was concomitant hematuria and proteinuria (31%). The most common histologic diagnoses were immunoglobulin A (IgA) nephropathy (23%), followed by focal segmental glomerulosclerosis (FSGS; 17%) and lupus nephritis (12%). Eleven percentage of them progressed to ESKD, of whom 87% received a kidney transplant (10% overall). Thirty percentage of the patients progressed to NRP and 5% died. Forty-seven percentage of our patients underwent MEB after diagnosis, and of these, 84% were not retained for further military service. Although IgA nephropathy was the most commonly diagnosed condition, FSGS and lupus nephritis diagnoses were significantly more likely to result in MEB.

Conclusions and Implications:
Immunoglobulin A nephropathy was the most frequent histologic diagnosis in active duty service members undergoing renal biopsy between 2005 and 2020. Despite being largely young and previously healthy, 11% progressed to ESKD and 5% died. A confirmed histologic diagnosis was associated with separation from the service and the end of military careers for 84% of the patients in the cohort who underwent MEB.
Kidney Diseases in Service Members

A subsequent international study evaluated the prevalence of glomerular diseases among patients sharing the same race and ethnicity but residing in different geographic locations. There was a significant variation in glomerular diseases by geographic location. Subsequent to the Portsmouth article, there have been no studies evaluating kidney biopsy results in an active duty cohort. Additionally, no studies have examined the overall health and military career outcomes following biopsy.

To this end, we retrospectively evaluated all native renal biopsies performed in active duty beneficiaries at the Walter Reed National Military Medical Center (WRNMMC) from 2005 to 2020. For this cohort, we determined renal biopsy indication, biopsy diagnosis, demographics, military status at the time of referral (including military rank and pay grade), and clinical/laboratory features (including serum creatinine, albuminuria, and proteinuria). We determined the time to end-stage kidney disease (ESKD), kidney transplantation, creatinine doubling, nephrotic-range proteinuria (NRP), and death. We also looked at the time to MEB following renal biopsy, which diseases predisposed soldiers to MEBs, and whether they were retained for military service. We also estimated the comparative costs for chronic kidney disease (CKD) management of new military recruits versus adding further screening tests to be performed in the recruitment process.

MATERIALS AND METHODS
This retrospective cohort study was reviewed and approved by the WRNMMC Institutional Review Board, with a waiver of informed consent (protocol no. WRNMMC-EDO-2020-0550). All native kidney biopsies performed on adult, active duty service members at WRNMMC between January 1, 2005, and November 24, 2020, were considered for inclusion. Open renal biopsies, transplant biopsies, and biopsies of individuals less than 18 years of age were excluded. Transplant biopsies and all non-percutaneous procedures were excluded in similar studies, so the same decision was made here. If a subject had multiple biopsies, only the first was included in the study. The WRNMMC Nephrology Fellowship program retains identifying information for all patients undergoing native and transplant kidney biopsy for fellowship accreditation purposes. Using this database, all percutaneous, native renal biopsies were identified, which totaled 459 cases. These cases were subsequently screened to determine if the patients were active duty service members at the time of their kidney biopsy. Of the 459 individuals, 169 met this criterion and were analyzed further.

The military healthcare network was used to obtain patient baseline and subsequent clinical and laboratory information. The healthcare network is composed of 9.6 million people with 65 hospitals and 412 clinics worldwide that have shared an electronic medical record (EMR) since 2005. We reviewed the comprehensive EMR (Armed Forces Health Longitudinal Technology Application and Joint Legacy Viewer), which includes EMR data from the Department of Veterans Affairs, for each potential case to assemble the active duty cohort.

Demographics, biopsy indication, family history of kidney diseases, personal history of diabetes and/or hypertension, military rank at the time of biopsy, body mass index, laboratory, histopathologic, and outcome data were collected and recorded for each biopsied subject. Renal biopsy indication was determined from the referring provider’s clinical note before the procedure, as well as the consult note placed to the interventional radiology service, where applicable. Military rank at the time of biopsy was determined using military demographic information in the EMR and prior clinical notes. Personal histories of diabetes and hypertension, as well as family history of kidney diseases, were determined by reviewing prior nephrology clinical notes. We recorded urine protein and microalbumin excretion from reports of protein-to-creatinine ratios (UPCRs) and spot microalbumin-to-creatinine ratios, respectively. Estimated glomerular filtration rate (eGFR) was determined using the creatinine-based CKD Epidemiology Collaboration equation, corrected for African American race as appropriate.

The follow-up period was extended until death, the last recorded patient encounter in Armed Forces Health Longitudinal Technology Application or Joint Legacy Viewer, or the end of the study on January 31, 2021. Death was determined using the EMR and verified using the Defense Suicide Prevention Office database. This database collects data on the deaths of all active duty soldiers (regardless of cause) and was used to confirm death in individuals identified on EMR review. It was also used to determine if any deaths had occurred which were not identified in the EMR. The cause of death was not specifically considered. Other outcomes included progression to ESKD, kidney transplantation, creatinine doubling from baseline, development of proteinuria greater than 3.5 g/day (NRP), and initiation and outcome of the MEB. The ESKD was defined by the initiation of kidney replacement therapy or preemptive kidney transplant. The MEB is a process where a service member is determined to either be fit or unfit for further service in the U.S. Military based on a specific medical condition, determined by regulation. We determined if the MEB had been initiated as well as found the result (retention or separation) for each subject by review of nephrology and social work notes in the EMR.

STATA MP/16.1 (College Station, TX) was used for all statistical analyses. Descriptive data are reported as a percentage, mean ± SD, or median (interquartile range) as appropriate. Univariate analyses were performed with chi-square testing for categorical variables. The t-test was used for continuous variables (Mann–Whitney test used for nonnormally distributed variables). P < .05 was considered statistically significant for all comparisons.

The probability of initiation of the MEB was estimated using the Kaplan–Meier method and log-rank test to assess for significant differences between the groups. The follow-up
RESULTS
Table I shows the baseline clinical and demographic characteristics of the cohort. The cohort (n = 169 subjects) consisted of predominantly Caucasian (81; 48%) and male (134; 79%) individuals. The mean age was 32 ± 9 years. The cohort was composed largely of enlisted service members (112; 67%) and the major military branch was the U.S. Army (82; 49%). The cohort was largely healthy, excluding the presence of kidney diseases, with 34% (57) having hypertension, 0.6% (1) diabetes, and 16% (27) with a family history of kidney diseases. Complete renal biopsy reports were available for all individuals. Mean follow-up time was 7.3 ± 9 years. The cohort was largely healthy, excluding the presence of kidney diseases, with 34% (57) having hypertension, 0.6% (1) diabetes, and 16% (27) with a family history of kidney diseases. Complete renal biopsy reports were available for all individuals. Mean follow-up time was 7.3 ± 4.8 years. The most common biopsy indication was concomitant hematuria and proteinuria (53; 31%), followed by nephrotic syndrome (37; 22%). The most common histologic diagnoses were immunoglobulin A (IgA) nephropathy (38; 23%), followed by FSGS (29; 17%) and lupus nephritis (20; 12%).

Patients with IgA nephropathy were predominantly Caucasian (31; 82%). Seventy-five percent (15) of patients with lupus nephritis and 59% (17) with FSGS were African Americans. Patients with membranous nephropathy were older (mean age: 38 ± 9.6 years) versus those with minimal change disease (mean age: 29 ± 7.1 years). Immunoglobulin A nephropathy was the most common histologic diagnosis for patients presenting with concomitant hematuria and proteinuria, hematuria alone, and acute nephritis. Minimal change disease was the most common histologic diagnosis for patients presenting with nephrotic syndrome, and FSGS the most common for those presenting with either non-NRP or CKD. Acute interstitial nephritis was the most common diagnosis for those with acute kidney injury.

Table II shows the clinical and military administrative outcomes of the cohort. Fifty-one patients (30%) progressed to ESKD, kidney transplantation, and initiation of the MEB, respectively. Six patients died, resulting in a 5% mortality rate. Of the individuals having the MEB initiated in our cohort, only 16% were retained for duty.

| Table I. Baseline Clinical and Demographic Characteristics of the Cohort at Diagnosis |
| Variables | Values |
| --- | --- |
| Age | Mean ± SD—years 32 ± 9 |
| Female sex—no. (%) | 35 (21%) |
| Race or ethnic group—no./total no. (%) | White 81/169 (48) |
| Hispanic or Latino | 12/169 (7) |
| Black | 62/169 (37) |
| Asian | 6/169 (4) |
| Pacific Islander | 5/169 (3) |
| Other | 3/169 (2) |
| Rank—no./total no. (%) | Junior enlisted (E1–4) 35/169 (21) |
| Senior enlisted (E5+) | 77/169 (46) |
| Junior officer (O1–4) | 28/169 (17) |
| Senior officer (O5–) | 19/169 (11) |
| Warrant officer | 3/169 (2) |
| Cadets | 7/169 (4) |
| Branch of service—no./total no. (%) | Army 82/169 (49) |
| Navy | 35/169 (21) |
| Air Force | 41/169 (24) |
| Marines | 10/169 (6) |
| Coast Guards | 1/169 (0.6) |
| Body mass index | Mean ± SD 28 ± 4 |
| Hypertension—no. (%) | 57 (34) |
| Type 2 diabetes—no. (%) | 1 (0.6) |
| Family history of renal disease—no. (%) | 27 (16) |
| Serum creatinine | Mean ± SD—mg/dL 2.0 ± 2.3 |
| Urine protein/creatinine ratio (g/g Cr) | Mean ± SD 2.4 ± 2.9 |
| Serum albumin | Mean ± SD—g/dL 3.5 ± 1.0 |
| Hemoglobin | Mean ± SD—g/dL 12.8 ± 2.2 |
| Hematuria—no. (%) | 136 (81) |
| Biopsy indication—no. (%) | Hematuria 11/169 (7) |
| Hematuria + proteinuria | 53/169 (31) |

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; IgA, immunoglobulin A; RPGN, rapidly progressive glomerulonephritis; SD, standard deviation.

*Miscellaneous diagnoses: advanced glomerulonephrosis, Alport’s syndrome, anti-glomerular basement membrane disease, C3 glomerulopathy, chronic tubulointerstitial disease, diffuse proliferative glomerulonephritis, Goodpasture’s disease, Henoch–Schoenlein purpura (IgA vasculitis), hypertensive nephrosclerosis, immunoglobulin M nephropathy, membranoproliferative glomerulonephritis, myeloma cast nephropathy, thin basement membrane disease, and thrombotic microangiopathy.
most common reasons for the MEB to be initiated. Of all kidney diseases, FSGS (19%; 24%), lupus nephritis, and IgA nephropathy, respectively, underwent the MEB. Of these individuals, 8%, 28%, and 8% of patients were retained following the MEB. Notably, five patients had acute tubular necrosis (ATN) on renal biopsy. Of these, two underwent the MEB. On Kaplan–Meier analysis, among the five most prevalent diagnoses, a higher proportion of patients with lupus nephritis and FSGS underwent the MEB ($P = .05$) (Fig. 1).

### DISCUSSION

In patients with renal diseases, kidney biopsy is required for accurate diagnosis, treatment decision-making, and determination of prognosis. This retrospective cohort study provides important information regarding the clinical outcomes and prognosis of active duty service members who are diagnosed with kidney diseases. In addition, there are no previous studies which evaluate both the results of kidney biopsies in active duty patients and their subsequent military career outcomes. The study cohort was composed of largely young and healthy individuals. Unlike the 1994 Portsmouth biopsy cohort, the most common histologic diagnosis was IgA nephropathy. Focal segmental glomerulosclerosis and lupus nephritis were the second and third most prevalent histologic diagnoses.

Forty-seven percentage of patients underwent the MEB and, of these individuals, only 16% were retained for duty. On average, patients had the MEBs initiated 1 year following renal biopsy. Among patients who underwent the MEB, the three most common diagnoses were FSGS, lupus nephritis, and IgA nephropathy. However, the disease with the largest percentage of patients who required the MEB was ANCA vasculitis, followed by FSGS and lupus nephritis. This information suggests that a substantial number of patients with biopsy-proven kidney diseases require the initiation of MEBs. This is consistent with the current guidelines followed by military physicians. For example, according to Army Regulation 40-501 (Standards of Medical Fitness), Chapter 3-19.c (1-10), individuals with CKD and eGFR less than 60 mL/min/1.73 m$^2$, and those with chronic or recurring nephritis or nephrotic syndrome, must be referred to the disability evaluation system for fitness for duty determination. Kidney transplant patients can be found fit for duty, but their potential assignment locations are restricted due to their medical care requirements. Individuals with advanced kidney diseases are thus unlikely to continue military service based on current guidelines. Notably, 40% of patients with ATN also underwent the MEB. Acute tubular necrosis is normally felt to be a benign and reversible condition, but biopsy is often not pursued unless there is failure to recover fully. Therefore, patients who required biopsy were more likely to have been left with CKD after their ATN episodes.

### TABLE II. Outcomes for the Cohort

| Outcome                                | No. (%) | Mean time to event ± SD—years |
|----------------------------------------|---------|------------------------------|
| Progression to creatinine doubling     | 22/140 (16)$^2$ | 5.2 ± 3.7                  |
| Progression to nephrotic-range proteinuria | 51/169 (30)$^2$ | 0.9 ± 2.2                 |
| Progression to ESKD                    | 16/140 (11)$^2$ | 4.3 ± 3.6                  |
| Progression to kidney transplant       | 14/141 (10)$^2$ | 7.1 ± 4.0                  |
| Progression to MEB$^2$                 | 75/159 (47)$^2$ | 1.0 ± 1.1                  |
| Retained for duty after MEB evaluation$^3$ | 12/73 (16)$^2$ | N/A                        |
| Death                                  | 6/128 (5)$^2$ | 9.0 ± 3.3                  |

Abbreviations: ESKD, end-stage kidney disease; MEB, medical evaluation board; SD, standard deviation.

### TABLE III. Medical Evaluation Board (MEB) Process in 78 Military Personnel Based on Biopsy Diagnosis$^4$

| Biopsy diagnosis—no./total no. (%) | Percentage of total number of MEB patients ($N = 78$) |
|-----------------------------------|------------------------------------------------------|
| IgA nephropathy                   | 12/78 (15)                                           |
| FSGS                              | 19/78 (24)                                           |
| Lupus nephritis                   | 13/78 (17)                                           |
| Membranous nephropathy            | 5/78 (6)                                             |
| Minimal change disease            | 5/78 (6)                                             |
| ANCA-associated vasculitis        | 5/78 (6)                                             |
| Acute interstitial nephritis      | 1/78 (1)                                             |
| Acute tubular necrosis            | 2/78 (3)                                             |
| Non-diagnostic                    | 3/78 (4)                                             |
| Undifferentiated glomerulonephritis | 1/78 (1)                                      |
| Normal                             | 1/78 (1)                                             |
| Miscellaneous$^a$                  | 11/78 (14)                                           |

Abbreviations: ANCA, anti-neutrophil cytoplasmic autoantibody; FSGS, focal segmental glomerulosclerosis; IgA, immunoglobulin A.

$^a$Miscellaneous diagnoses: advanced glomerulosclerosis, Alport’s syndrome, anti-glomerular basement membrane disease, C3 glomerulopathy, chronic tubulointerstitial disease, diffuse proliferative glomerulonephritis, Goodpasture’s disease, Henoch–Schönlein purpura (IgA vasculitis), hypertensive nephrosclerosis, Immunoglobulin M nephropathy, membranoproliferative glomerulonephritis, myeloma cast nephropathy, thin basement membrane disease, and thrombotic microangiopathy.

Tables III describes the 78 service members who had MEBs initiated for kidney diseases following biopsy. Three patients were not included in the analysis for MEBs as an outcome because of the timing of their renal biopsy. Two individuals had renal biopsies performed before the initiation of the MEB and one patient had their MEB started the day of their biopsy. Of all kidney diseases, FSGS (19%; 24%), lupus nephritis (13; 17%), and IgA nephropathy (12; 15%) were the most common reasons for the MEB to be initiated.

Supplemental Table SI describes the percentages of individuals with a specific diagnosis from renal biopsy who underwent the MEB. Based on our analysis, the kidney disease most likely to lead to the MEB was anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis, with 83% of the patients receiving this diagnosis ultimately having the MEB initiated. Ultimately, 66%, 65%, and 33% of patients with FSGS, lupus nephritis, and IgA nephropathy, respectively, underwent the MEB. Of these, 8%, 28%, and 8% of patients were retained following the MEB.

### Abbreviations

ESKD, end-stage kidney disease; MEB, medical evaluation board; SD, standard deviation.
Despite the young ages and lack of comorbid medical conditions, 11% of the cohort met these criteria for ESKD classification and 10% of the cohort received a kidney transplant. The percentage of patients meeting ESKD criteria (and later being transplanted) is significant considering the potential healthcare costs. According to Saran et al., the average cost per patient per year for care of a veteran with CKD 3a between 21 and 65 years of age ranged from $15,985 to $18,514. Cost increased to $21,231-$29,756, $37,347-$44,556, and $58,341-$69,897 for the care of CKD 3b, CKD 4, and CKD 5 patients, respectively.\(^7\) Epidemiologic data from Kaiser Permanente note the annualized mean medical costs in total for CKD patients, adjusted for age, sex, and race/ethnicity, ranged from $6,746 to $8,003 per patient. These individuals did not have diabetes, cardiovascular disease, or heart failure and 76% of these patients were categorized in the CKD 3a group.\(^8\) After initiation of dialysis, healthcare costs increase significantly. According to the U.S. Renal Data System 2019 Report, in 2017, Medicare patients on intermittent hemodialysis between the ages of 22 and 64 years of age had an average cost per patient per year of $88,921-$91,747. Those who underwent kidney transplant had an average cost per patient per year of $36,803-$46,146.\(^9\)

Basic metabolic panels (BMPs) and UPCRs are $28-33 and $49-58, respectively.\(^10\) According to the U.S. Army’s 2018 recruiting facts, the regular army had 69,972 new recruits.\(^11\) Oliver et al. found that in 2015, the prevalence of CKD among active duty service members was 0.7%, which means that as many as 4,898 of the newly recruited soldiers in the year 2018 potentially had CKD on entry to the U.S. Army.\(^12\) The cost to test all the new military recruits for CKD using BMP and UPCR would be approximately $5,387,844-$6,367,452 annually. The minimal annual cost of caring for the 4,898 new recruits in 2018 with potentially undiscovered CKD at the time of their entry into the military would be approximately $33,041,908, if it is assumed that all had CKD 3a disease. The annual cost of care would significantly increase as CKD progresses, if any are initiated on dialysis, or if any have a kidney transplantation. These figures suggest there may be cost benefit to adding additional measures (i.e., performing BMPs and UPCRs) to screen new recruits for CKD before entrance into the military.

A large proportion of ESKD patients in the study cohort (87%) ultimately received a kidney transplant. This is considerably higher than the 2016 national average for receiving a deceased donor kidney transplant within 1 year of ESRD initiation, which ranged from 12.5% to 33.8% for individuals 22-64 years of age. This is also higher than the 2017 kidney transplantation rates for patients between the ages of 22 and 64 years, which were 3.7-12 per 100 dialysis patient years.\(^9\) This may highlight the benefits garnered from being prepared and listed for kidney transplant within the military and the Veterans Affairs medical systems, which have been shown to have superior outcomes for patients with ESKD and kidney transplant.\(^13-15,17,18\)

The strengths of this study include the size of the cohort, the duration the cohort patients were followed, and the detailed demographic, clinical, and outcome information. Potential limitations include that the cohort was drawn from a single referral center, the exclusion of open and computed tomography–guided native renal biopsies, the possibility of loss to follow-up, and undocumented outcomes. Additionally, we did not address the effects of specific patient-centered therapies on the outcomes of our cohort because this was not
the aim of our study nor was it included in our original Institutional Review Board proposal. This would be an excellent follow-up study and one that will potentially be pursued. Further, the requirement for biopsy in our patient cohort may suggest more severe kidney diseases and thus may portend a worse prognosis in regard to the risk of ESKD.

This study demonstrates the spectrum of kidney diseases among active duty service members requiring kidney biopsy at our institution and the impact on health and career outcomes. Specifically, primary kidney disease diagnoses led to the MEBs and ultimately the removal of many active duty service members in the study. Despite the young age and lack of medical comorbidities, 11% of the cohort met criteria for ESKD, which highlights the poor prognosis of glomerular diseases and the need that these diseases be recognized and treated by a specialist. Most of the patients who were initiated on intermittent dialysis ultimately underwent kidney transplantation and the percentage was significantly larger than the national average. We also estimated the healthcare costs associated with glomerular diseases and CKD, and the potential cost benefits of screening all military recruits for kidney diseases before entry into the army.

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SUPPLEMENTARY MATERIAL

Supplementary material is available at Military Medicine online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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