Racial disparities in patients diagnosed with light chain (AL) amyloidosis

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Dear Editor,

Light chain (AL) amyloidosis arises from a precursor plasma cell neoplasm that produces clonal free light chains that form insoluble fibril deposits leading to organ dysfunction1. Because the disease is rare, heterogeneous, and multi-systemic, it can take several months to years for the symptoms to show in patients before a diagnosis is made2. Knowledge of the pre-existing clinical characteristics of patients eventually diagnosed with AL amyloidosis is critical as it may inform early diagnosis of the disease. Evidence suggests that early diagnosis of AL amyloidosis leads to improved outcomes, including superior survival, as the disease can be modulated with recently available therapies3,4. Among diagnosed amyloidosis patients, Black men and women have the highest mortality rate5. Although existing literature has documented a racial predisposition in plasma cell disorders, such as monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma6,7, racial differences in the incidence of the multiple other potential clinical precursor diagnoses associated with AL amyloidosis remain unknown. In this report, we use nationally representative electronic health records (EHR) data to document and contrast the clinical characteristics of patients diagnosed with AL amyloidosis by self-reported race. We also compare the clinical characteristics between patients with AL amyloidosis and matched individuals without amyloidosis by race. We hypothesized that differences in AL-associated, pre-existing diagnoses will be evident in patients prior to their diagnosis of AL amyloidosis and that these differences will vary by the patients’ race.

Data for this analysis were drawn from TriNetX, a health research network providing access to high-quality de-identified patient-level data from EHR from large healthcare organizations. These data, which are refreshed on a regular basis, are made available through a research network that provides a HIPAA compliant platform with a built-for-purpose user interface and analytics capabilities. No protected health information or personal data is made available to the users of the platform. For this analysis, the TriNetX platform with browser-based real-time analytical features was used.

**Patient population:** Patients were coded to have AL amyloidosis if they (i) had two or more occurrences of diagnosis codes ICD10: E85.81, E85.4, E85.89, or E85.9 between Jan 1, 2010 and Dec 31, 2019 and (ii) received specific treatment after their AL amyloidosis diagnosis. Specific treatment included the use of one or more of the following: bendamustine, bortezomib, carfilzomib, cyclophosphamide, daratumumab, dexamethasone, doxorubicin, elotuzumab, etoposide, interferon alpha-2a/2b, ixazomib, lenalidomide, melphalan, panobinostat, pomalidomide, prednisone, prednisolone, thalidomide, vincristine, or transfusion of autologous hematopoietic cells. The sample was further restricted to individuals aged 40 or older due to the low incidence of the disease in younger adults. The cohort of AL amyloidosis patients was then stratified by race as African American/Black and White. The two comparison groups of Black and White patients without amyloidosis comprised individuals who (i) did not have any ICD code for AL diagnoses and (ii) had at least two visits with the healthcare system in the time period of Jan 1, 2010–Dec 31, 2019. To ensure the comparability of the comparison groups, we further restricted the cohorts to those who had at least one visit in 2019.

Pre-existing diagnoses were defined using diagnostic codes of interest present in an AL amyloidosis patient prior to the diagnosis of AL amyloidosis. These were...
grouped within four major categories: cardiac, renal, gastrointestinal/hepatic, other. For example, the cardiac category included diagnostic codes for cardiomyopathy, heart failure, cardiac arrhythmias, etc. The specific codes considered are provided in the tables.

**Statistical analyses:** We used t-tests to compare the clinical characteristics of Black and White AL amyloidosis patients after matching for age, sex, and presence of type 2 diabetes. We matched with diabetes as some AL-associated diagnoses, e.g., cardiomyopathy, heart failure, proteinuria, chronic kidney disease, and neuropathy, may overlap with diabetes and there is a known racial difference in the prevalence of diabetic complications. We performed 1:1 matching based on the greedy nearest-neighbor matching algorithm using caliper of 0.1 pooled standard deviations (SD). The same methodology was used to compare the pre-existing clinical characteristics of patients with and without a diagnosis of AL amyloidosis by race.

A total of 4028 patients were identified as having a diagnosis of AL amyloidosis during the study period. Among Black patients with AL amyloidosis (N = 695), the mean age was 65 (SD 11) years with 55% males. The geographic distribution included 16% Northeast, 23% Midwest, 56% South, and 5% West. Among 3333 identified White patients, the mean age was 67 years (SD 11) with 58% male. The geographic distribution included 17% Northeast, 24% Midwest, 41% South, 17% West, and 1% unknown. The age difference by race appeared smaller in AL compared to MGUS. After 1:1 matching, 691 Black AL patients matched with 691 White AL patients.

Compared to White AL patients, Black patients were more likely to have pre-existing MGUS as well as multiple other cardiac, renal, gastrointestinal AL-associated diagnoses, and carpal tunnel syndrome preceding the formal diagnosis of AL amyloidosis (Table 1). The difference in pre-existing MGUS was different (21% Black vs 13% White, p = 4.48E−05) but pre-existing multiple myeloma was not different between the two groups (32.4% Black vs 30.83% White, p = 0.53). This may suggest that once multiple myeloma is diagnosed, patients are in the care of specialists who may be vigilant for identification of amyloidosis and there is no racial difference in this diagnosis. The magnitude of differences was particularly striking for the diagnoses of cardiomegaly (28.51% vs 20.55%, p 0.0006), cardiomyopathy (37.19% vs 22.58%, p 2.93E−09), heart failure (54.85% vs 33.29%, p 6.85E−16), and chronic kidney disease (43.56% vs 35.02%, p 0.001), for Black compared to White patients, respectively. These clinical conditions are known harbingers of worse outcomes in AL amyloidosis. These findings raise concerns that Black patients with AL amyloidosis may be diagnosed later in the disease process. These findings also suggest that it may take longer or require a greater constellation of AL-associated symptoms/diagnoses before AL amyloidosis to be diagnosed in Black patients relative to White individuals. It is well known that patients with AL see multiple physicians including subspecialists for various diagnoses, e.g., proteinuria, carpal tunnel syndrome, cardiomyopathy, related to the amyloidosis diagnosis, and our results suggest that race can be associated with AL amyloidosis diagnosis.

To shed further light on the racial differences in AL amyloidosis, we examined the extent to which pre-existing diagnoses differ by race among patients with and without AL amyloidosis. Table 2 shows the results of this analysis applied to samples matched by age, sex, and presence of type 2 diabetes, which yielded 695 Black patients and 3333 White patients without AL amyloidosis. As expected, there was a significantly higher incidence of MGUS, as well as more other AL-associated organ-specific and other pre-existing diagnoses of interest preceding the diagnosis of AL amyloidosis within each racial group, the prevalence of which was considerably higher among Black patients with AL. This pattern confirms the notion that AL patients have a different clinical profile than those who do not develop the disease. These findings also suggest that it may be possible to develop an early warning system through advanced statistical models that would identify patients at risk for developing AL amyloidosis earlier in the disease course. Additionally, there was a higher prevalence of AL-associated pre-existing conditions among the subgroup of African American/Black individuals without AL when compared to their White counterparts, pointing to a higher burden of comorbidities or a higher proportion of undiagnosed AL amyloidosis in Black individuals compared to Whites. Staron, et al. recently reported that among patients seen at an Amyloid Center of Excellence, Black patients had a more aggressive phenotype. Additionally, other systemic barriers and social determinants of health may further result in delays/exclusion of AL amyloidosis patients being referred to centers of excellence, thus resulting in additional race-based disparities in AL amyloidosis care, which needs to be further explored.

Our study is limited by the lack of granular data on AL amyloidosis, including the lack of information on stage and biomarkers. Nonetheless, these large, nationwide EHR data provide a valuable opportunity to understand the clinical burden of AL amyloidosis. These data also suggest that AL is not as rare even with our conservative definition using diagnostic codes. Our findings are consistent with the hypothesis that Black patients may experience under- or delayed diagnosis, as suggested by their higher burden of pre-existing, AL-associated diagnoses prior to the formal AL diagnosis. This is especially true for critical organ conditions associated with early mortality. Finally, there are significant differences, overall and across racial groups, in the prevalence of pre-existing
Table 1  Comparison of pre-existing diagnoses in AL amyloidosis by race.

| ICD code | Pre-existing diagnosis                          | Black, with AL N = 691 | White, with AL N = 691 | p-value     | SD   |
|----------|-----------------------------------------------|------------------------|------------------------|-------------|------|
| D47.2    | MGUS                                          | 21.13%                 | 12.88%                 | 4.48E−05    | 0.22 |
| C90      | Multiple myeloma                              | 32.42%                 | 30.83%                 | 0.53        | 0.03 |

**Cardiac diagnoses**

| I51.7    | Cardiomegaly                                  | 28.51%                 | 20.55%                 | 0.0006      | 0.19 |
| I42      | Cardiomyopathy                                | 37.19%                 | 22.58%                 | 2.93E−09    | 0.32 |
| I49      | Other cardiac arrhythmia                      | 30.25%                 | 19.68%                 | 5.7E−06     | 0.25 |
| R06.0    | Dyspnea                                       | 49.78%                 | 35.17%                 | 3.88E−08    | 0.30 |
| R55      | Syncope and collapse                          | 13.46%                 | 9.70%                  | 0.03        | 0.12 |
| R42      | Dizziness and giddiness                       | 14.33%                 | 14.62%                 | 0.88        | 0.01 |
| R60      | Edema                                         | 33.58%                 | 26.77%                 | 0.006       | 0.15 |
| I50      | Heart failure                                 | 54.85%                 | 33.29%                 | 6.85E−16    | 0.45 |
| J90      | Pleural effusion                              | 11.43%                 | 11.72%                 | 0.87        | 0.01 |
| I48      | Atrial fibrillation and flutter               | 21.85%                 | 21.85%                 | 1           | 0    |
| I95      | Hypotension                                   | 21.71%                 | 18.67%                 | 0.16        | 0.08 |

**Renal diagnoses**

| N04,     | Nephrotic syndrome                            | 8.39%                  | 9.84%                  | 0.35        | 0.05 |
| R80      | Proteinuria                                   | 23.16%                 | 19.97%                 | 0.15        | 0.08 |
| N18      | Chronic kidney disease                        | 43.56%                 | 35.02%                 | 0.001       | 0.18 |

**Neurological diagnoses**

| N52.9    | Male erectile dysfunction                     | 7.67%                  | 4.34%                  | 0.009       | 0.14 |
| M79.2    | Neuralgia and neuritis                        | 2.17%                  | 2.61%                  | 0.60        | 0.03 |
| R20      | Disturbances of skin sensations               | 13.89%                 | 11.00%                 | 0.10        | 0.09 |
| G60      | Hereditary and idiopathic neuropathy          | 12.59%                 | 10.42%                 | 0.21        | 0.07 |
| G62      | Other and unspecified polyneuropathies       | 11.72%                 | 11.29%                 | 0.80        | 0.01 |
| G90      | Disorders of autonomic nervous system         | 2.75%                  | 3.47%                  | 0.44        | 0.04 |

**GI/Hepatic diagnoses**

| R13.1    | Dysphagia                                     | 12.88%                 | 9.70%                  | 0.06        | 0.10 |
| R16      | Hepatomegaly and splenomegaly                | 5.79%                  | 5.79%                  | 1           | 0    |
| K76      | Other diseases of liver                       | 13.17%                 | 11.00%                 | 0.22        | 0.07 |
| R11      | Nausea and vomiting                           | 19.83%                 | 16.35%                 | 0.09        | 0.09 |
| K59.0    | Constipation                                  | 22.00%                 | 14.76%                 | 0.0005      | 0.19 |
| R19.7    | Diarrhea                                      | 15.63%                 | 17.95%                 | 0.25        | 0.06 |
| R10      | Abdominal pain                                | 27.50%                 | 19.25%                 | 0.0003      | 0.20 |

**Other diagnoses**

| R53      | Malaise and fatigue                           | 30.83%                 | 30.39%                 | 0.86        | 0.01 |
| G56.0    | Carpal Tunnel Syndrome                        | 11.14%                 | 7.24%                  | 0.01        | 0.14 |
| D69      | Purpura                                       | 15.20%                 | 14.47%                 | 0.71        | 0.02 |
| Q38      | Macroglossia                                  | 2.32%                  | 1.45%                  | 0.24        | 0.06 |

Patients matched by age, sex, and presence of diabetes mellitus.
SD standard difference.
| ICD10 code | Pre-existing diagnosis                          | Black, with AL N = 695 | Black, no AL N = 695 | p-value Black, AL vs not | SD  | White, with AL N = 3333 | White, no AL N = 3333 | p-value White, AL vs not | SD  |
|-----------|-----------------------------------------------|------------------------|----------------------|--------------------------|-----|-------------------------|------------------------|--------------------------|-----|
| D47.2     | MGUS                                          | 21.01%                 | 1.44%                | 6.84E−31                 | 0.65| 16.41%                  | 0.36%                  | 0                        | 0.61|
| C90       | Multiple myeloma                               | 32.23%                 | 1.44%                | 6.84E−31                 | 0.90| 32.67%                  | 0.30%                  | 0                        | 0.97|

**Cardiac diagnoses**

| I51.7 | Cardiomegaly | 28.92% | 9.35% | 1.81E−20 | 0.51 | 20.13% | 4.08% | 0.51 |
| I74.2 | Cardiomyopathy | 37.41% | 5.04% | 0.86 | 23.19% | 2.70% | 0.64 |
| I49 | Other cardiac arrhythmia | 30.50% | 10.50% | 2.59E−20 | 0.51 | 22.05% | 8.16% | 0.40 |
| R06.0 | Dyspnea | 50.07% | 21.73% | 3.24E−20 | 0.51 | 20.13% | 4.08% | 0.51 |

**Renal diagnoses**

| N04 | Nephrotic syndrome | 8.35% | 1.44% | 2.30E−09 | 0.32 | 10.08% | 0.30% | 0.45 |
| N80 | Proteinuria | 23.31% | 4.17% | 3.70E−25 | 0.58 | 19.92% | 2.13% | 0.59 |
| N18 | Chronic Kidney disease | 43.89% | 14.53% | 2.38E−33 | 0.68 | 33.15% | 6.48% | 0.71 |

**Neurological diagnoses**

| N52.9 | Male erectile dysfunction | 7.63% | 9.07% | 0.323233 | 0.05 | 4.50% | 4.71% | 0.68 |
| M79.2 | Neuralgia and Neuritis | 2.30% | 3.31% | 0.2555555 | 0.06 | 3% | 1.29% | 1.45E−06 |
| R20 | Disturbances of skin sensations | 13.96% | 8.49% | 0.001 | 0.17 | 14.13% | 7.26% | 1.13E−19 |
| G60 | Hereditary and idiopathic neuropathy | 12.81% | 3.02% | 1.41E−11 | 0.37 | 10.77% | 2.10% | 0.36 |
| G62 | Other and unspecified polyneuropathies | 11.66% | 4.17% | 2.38E−07 | 0.28 | 12.51% | 3.78% | 8.26E−39 |
| G90 | Disorders of autonomic nervous system | 2.73% | 1.44% | 0.001225 | 0.09 | 3.24% | 0.30% | 0.82E−20 |

**GI/hepatic**

| R13.1 | Dysphagia | 12.81% | 6.19% | 2.57E−05 | 0.23 | 9.84% | 5.19% | 5.99E−13 |
| R16 | Hepatomegaly and splenomegaly | 5.76% | 1.73% | 7.57E−05 | 0.21 | 4.35% | 1.56% | 1.74E−11 |
| K76 | Other diseases of liver | 13.38% | 6.91% | 6.39E−05 | 0.22 | 9.15% | 4.56% | 1.21E−13 |
| R11 | Nausea and vomiting | 20% | 11.66% | 2.02E−05 | 0.23 | 15.51% | 7.29% | 4.61E−26 |
| K59.0 | Constipation | 22.16% | 12.81% | 4.43E−06 | 0.25 | 14.67% | 6.45% | 9.31E−28 |
| R19.7 | Diarrhea | 15.54% | 6.76% | 2.01E−07 | 0.28 | 15.27% | 6.90% | 1.37E−27 |
| R10 | Abdominal pain | 27.63% | 24.60% | 0.20 | 0.07 | 20.16% | 17.01% | 0.001 | 0.08 |
| ICD10 code | Pre-existing diagnosis         | Black, with AL N = 695 | Black, no AL N = 695 | p-value Black, AL vs not | SD White, with AL N = 3333 | White, no AL N = 3333 | p-value White, AL vs not | SD  |
|-----------|-------------------------------|------------------------|----------------------|--------------------------|-----------------------------|--------------------------|--------------------------|-----|
| R53       | Malaise and fatigue           | 30.79%                 | 18.56%               | 1.24E-07                 | 0.29                        | 32.73%                   | 15.12%                   | 0.42|
| G56.0     | Carpal Tunnel Syndrome        | 11.08%                 | 4.17%                | 1.23E-06                 | 0.26                        | 8.34%                    | 3.36%                    | 0.21|
| D69       | Purpura                       | 15.25%                 | 3.45%                | 4.23E-14                 | 0.41                        | 12.90%                   | 2.82%                    | 0.38|
| K14.8     | Macroglossia                  | 2.30%                  | 0%                   | 5.74E-05                 | 0.22                        | 1.44%                    | 0.30%                    | 5.40E-07 | 0.12 |

Patients matched by age, sex, and presence of diabetes mellitus. SD standard difference.

diagnoses in individuals with and without AL, suggesting the feasibility and value of developing predictive algorithms aimed at identifying patterns of precursor conditions associated with the likelihood of an AL amyloidosis diagnosis. These results highlight significant racial disparities in AL amyloidosis diagnosis. Our next steps include studying differences in the length of time for pre-existing diagnoses prior to AL diagnosis as well outcomes after the diagnosis, including the burden of illness. Future work is also needed to study the causes and consequences of racial disparities on the disease course and mortality of AL amyloidosis patients.

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All authors contributed toward study design, analysis, review of the findings, and manuscript writing.

Conflict of interest
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