Carpal Tunnel Syndrome and Other Predictors of Amyloidosis

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INTRODUCTION: Amyloidosis is a protein misfolding disease caused by extracellular deposits of amyloid fibrils. As the amyloid protein aggregates, it becomes insoluble and causes organ dysfunction. (1) There are two main types of amyloidosis: amyloid transthyretin (ATTR) and immunoglobulin light chain (AL). Both ATTR and AL amyloidosis can impact cardiac tissue, resulting in fatal disease. (1) Studies have shown that carpal tunnel patients, particularly older adults, may have amyloid deposits in their flexor tenosynovium, but have not yet demonstrated any overt signs of amyloidosis. (1) In an effort to understand risk factors for amyloidosis, a study identified several "red-flag" symptoms and patient characteristics, and placed them in two tiers, based on their predictive value. (2) However, this study did not rank these "red flags" by their individual predictive value. In this study, we used the TriNetX database to assess the relative predictability of each "red flag" so that the risk of a carpal tunnel syndrome patient having undiagnosed amyloidosis could be more accurately assessed before recommending a tenosynovial biopsy at the time of carpal tunnel release.
METHODS: This was a retrospective cohort study of patients with carpal tunnel syndrome (CTS), amyloidosis, and various other "red flag" diagnoses. TriNetX contains de-identified data, and therefore, this study was exempt from our Institutional Review Board. The study included electronic medical record (EMR) data from patients included in the TriNetX Research Network as of August 17, 2025. All cohorts were composed of patients with the given diagnoses between January 1, 2010, and December 31, 2019. The CTS cohort included patients with a diagnosis code of carpal tunnel syndrome, but no prior diagnosis of amyloidosis. The amyloidosis cohort included patients with neuropathic heredofamilial amyloidosis, organ-limited amyloidosis, light chain amyloidosis, or wild-type transthyretin-related amyloidosis. For the cohorts that examined pre-existing risk factors before the CTS diagnosis in patients aged ≥50, all cohorts included patients with CTS but excluded patients who had any prior diagnosis of amyloidosis. The following pre-existing risk factors were examined: African American race, heart failure, trigger finger, diabetes mellitus type 2, atrial fibrillation, aortic stenosis, cardiomyopathy or chest pain, CTS surgical release, endoscopic CTS surgical release, open CTS surgical release, peripheral neuropathy, lumbar spinal stenosis, total knee arthroplasty, total hip arthroplasty, rotator cuff tear, family history of heart disease, sleep apnea, vertigo, essential hypertension, bilateral CTS, shortness of breath, localized edema, low back pain, diabetes mellitus type 1, digestive issues or abnormal weight loss, floaters, enlarged tongue, diabetic neuropathy, and Dupuytren's contracture. Using the compare cohorts feature on TriNetX, each comparison was analyzed after 1:1 propensity score matching for age at index event. The index event was defined as the diagnosis of CTS. For each comparison, the risk of developing amyloidosis in the CTS cohort without the additional risk factor was subtracted from the risk in the CTS cohort with the additional risk factor to yield the risk difference. The risk difference was then scaled to reflect a population of 100,000.
RESULTS SECTION: The overall population included in TriNetX consists of 144,092,751 patients across 103 healthcare organizations (HCOs). The prevalence of these conditions in the overall TriNetX population is as follows: 800,662 subjects (0.556%) for CTS and 23,350 subjects (0.016%) for amyloidosis. For the males aged ≥50, as shown in Figure 1, 18 of the 29 pre-existing risk factors significantly increased the risk of developing amyloidosis within six years following a CTS diagnosis. For the females aged ≥50, data not shown, 20 of the 29 pre-existing risk factors significantly increased the risk of developing amyloidosis within six years following a CTS diagnosis. However, the range of the absolute risk difference was lower than that seen in males, with the highest risk factor also found to be heart failure though with a lower number of 261 per 100,000 compared to 702 per 100,000.
DISCUSSION: For both males and females with CTS, there are several pre-existing conditions associated with an increased risk of developing amyloidosis within six years of the initial CTS diagnosis. These additional risk factors may identify high-risk patients that should be recommended for a tenosynovial biopsy at the time of their CTS surgical release. These results build upon prior studies by ranking comorbidities and drawing from patient populations that are significantly larger, with most cohorts consisting of ≥5,000 subjects, giving this study an unsurpassed level of power. Hand surgeons can use these ranked pre-existing conditions as a diagnostic tool to screen and identify their CTS patients that should be recommended to have a tenosynovial biopsy. The hand surgeon can now better understand how each individual risk factor increases the risk of their CTS patient developing amyloidosis.
SIGNIFICANCE/CLINICAL RELEVANCE: If asymptomatic amyloid patients with carpal tunnel syndrome can be identified early, then new drugs can potentially slow the deposition of amyloid in major organs. Therefore, taking a sample of a patient's tenosynovium during carpal tunnel surgery who are at risk with these red flags for amyloidosis is important and potentially lifesaving.
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2. JP D, M H, BW S, WH S. Carpal Tunnel Syndrome: A Potential Early, Red-Flag Sign of Amyloidosis - PubMed. The Journal of hand surgery. 2019 Oct;44(10).

IMAGES AND TABLES:

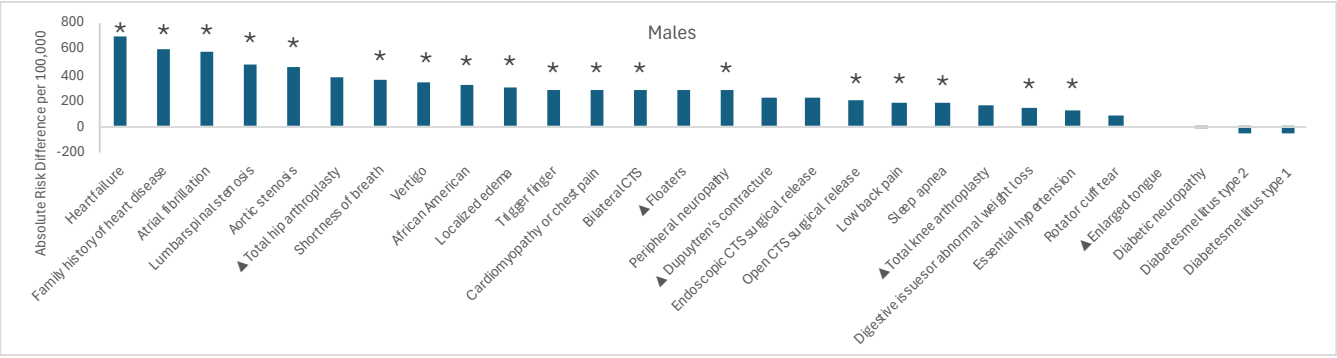

Fig. 1 Risk difference per 100,000 of developing amyloidosis within the six years following CTS diagnosis in males aged ≥50. The risk factors are listed strongest to weakest based on risk difference. Asterisks indicate a statistically significant p value with $p < 0.05$. A triangle next to a pre-existing risk factor (▲) indicates a cohort population <5,000.

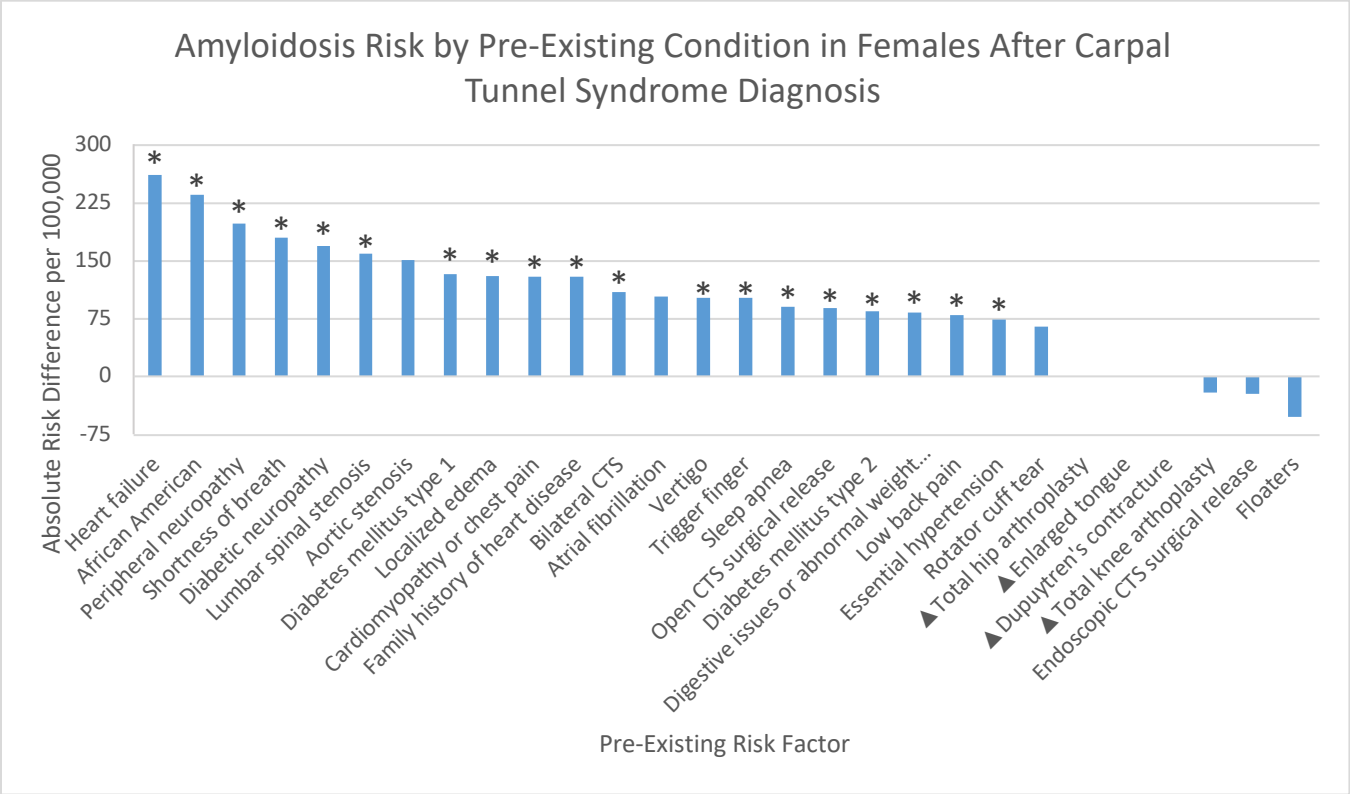

Fig. 1B Risk difference per 100,000 of developing amyloidosis within the six years following CTS diagnosis in females aged ≥50. The risk factors are listed strongest to weakest based on risk difference. Asterisks indicate a statistically significant p value with $p < 0.05$. A triangle next to a pre-existing risk factor (▲) indicates a cohort population <5,000.