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# Racial Differences in Transthyretin Cardiac Amyloidosis: A Systematic Review of Genotype, Diagnosis, Treatment, and Outcomes

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**Systematic Review**

**Keywords:** Transthyretin Amyloidosis, Cardiac Amyloidosis, Ethnicity, Genetic Variation, Genotype, Diagnosis, Therapeutics, Treatment Outcome

**Posted Date:** November 22nd, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-11275027/v1

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**Additional Declarations:** No competing interests reported.

## Abstract

# Background

Transthyretin (TTR) amyloidosis, a form of Cardiac Amyloidosis, is characterized by gradual accumulation of TTR, disrupting the anatomy and physiology of various organs, especially the heart; it has increasingly become a common cause of cardiac failure, morbidity, and mortality. Different genetic variants have been identified that are influenced by race and ethnicity, and the existing evidence affects treatment and clinical outcomes. However, the extent of this influence on the genetic variant is not fully understood.

# Methods

The review protocol was registered with PROSPERO (CRD420261404519) and conducted in line with PRISMA 2020 guidelines. Six electronic databases were searched between June and July 2026: PubMed/MEDLINE, Embase, ClinicalTrials.gov, CINAHL, ScienceDirect, and Cochrane Central Register of Controlled Trials (CENTRAL), and 1,073 studies were retrieved. Following removal of duplicates, studies reporting race and ethnicity in confirmed ATTR-CM were included, and two independent reviewers screened the studies, assessed the risk of bias, and extracted the data. Data were synthesized narratively due to significant methodological differences.

# Results

941 out of 1,073 were screened, and 78 studies underwent full-text screening. 9 studies met the inclusion criteria. These studies showed a complex interplay between race/ethnicity and genetic carriage in transthyretin cardiac amyloidosis. p.V1421 mutations were significantly higher in black patients (79%) compared to white patients (1%). Invasive diagnostic tests are more common among the black patients compared to white counterparts (62.3 vs 17.7%), non - invasive techniques such as bone scintigraphy are more common with white patients (70.6% p = 0.016). Black patients with ATTRwt-CA, compared with non-black patients, received significantly lower disease-modifying therapy (68.4% vs 88.4%). More advanced forms of the disease, with higher risk of mortality, thromboembolism, heart failure, and frequent hospitalization, are more common with the black and Afro-Caribbean patients, although the disparities were absent or attenuated in some studies with more equitable access to treatment.

# Conclusion

Differences in race and ethnicity do exist in patients with confirmed ATTR-CM and involve genetic, diagnostic, and clinical outcomes. Genetic factors alone cannot fully explain these disparities and may reflect socioeconomic disadvantage and unequal healthcare access. Large multicenter studies are needed to explain these mechanisms and identify ways to reduce these disparities.

## 1. Introduction

Cardiac Amyloidosis (CA) is an emerging cause of death and morbidity globally, caused by the deposition of insoluble fibrils formed from misfolded amyloid proteins [1]. While there are different types of amyloidosis, Transthyretin (TTR) amyloidosis (also known as ATTR amyloidosis) is an increasingly recognized, slowly progressive, life-threatening condition characterized by the gradual accumulation of TTR (a plasma protein synthesized in the liver) in organs throughout the body. This accumulation disrupts the anatomy and physiology of affected tissues, particularly the heart, and is a significant contributor to mortality. Cardiac deposition of amyloid leads to impaired myocardial contraction and relaxation due to expansion of the extracellular space [2].

Wild-type amyloidosis (ATTRwt), formerly referred to as senile systemic amyloidosis, is the most prevalent form. It primarily manifests as a cardiomyopathic phenotype (ATTR-CA) resulting from age-related dysfunction of homeostatic mechanisms and typically progresses slowly. ATTRwt predominantly affects males and older adults [2, 3]. Hereditary or variant ATTR (ATTRv), the second subtype, is an autosomal-dominant disease caused by mutations in the transthyretin (TTR) gene located on chromosome 18, with about 130 pathogenic mutations. This subtype is rapidly progressive and highly heterogeneous, with some variants having predominantly cardiac disease, some neuropathy, and some mixed phenotypes with variable ages of onset [2]. This phenotypic heterogeneity results from key factors, such as specific TTR mutations, regional location, inheritance pattern, age at onset, and localized prevalence patterns.

Recent evidence indicates that differences in genetic ancestry, disease presentation, and clinical outcomes contribute to variation in the diagnosis and management of ATTR-CA across racial and ethnic groups. Non-genetic factors, including socioeconomic status, access to specialists, referral patterns, and clinician awareness of ATTR-CA, also influence the timeliness of diagnosis, treatment, and clinical outcomes among these populations.

Notably, several ATTRv mutations have been linked to disparities in clinical presentation among patients globally. The Val122Ile, also known as Val1421Ie, is the most common subtype of ATTRv, found in West Africa, France, and the United States, and largely affects males and older adults [4]. The Ala97Ser genotype is predominant in individuals of Chinese descent in Malaysia and Taiwan [5]. Val30Met is found in Portugal and Sweden, with characteristic early- and late-onset presentations, respectively. Thr60Ala has also been noted in the United Kingdom and Ireland, occurring mostly in middle-aged individuals [2].

The high variability in both penetrance and age of onset across populations has been associated with the clustering of mutations by ethnicity and geographic location, due to migration across countries and continents, a phenomenon known as the ‘founder effect' [2]. Over the years, the diagnostic gold standard has been endomyocardial biopsy (EMB), but this has been limited by restricted access to diagnostic centers and the unavailability of expertise for tissue interpretation and monitoring. Recently, bone-avid radionuclide scintigraphy has become an important non-invasive diagnostic approach for ATTR-CA. A

positive scan can support a non-biopsy diagnosis when a plasma-cell disorder underlying AL amyloidosis has been excluded [6]. However, diagnostic variability is pronounced across races, with a median of 17 tests per patient before arriving at the correct diagnosis [2].

Several approaches for management of ATTR-CA have been explored. Tafamidis, a transthyretin stabilizer, was the first approved medication by the Food and Drug Administration (FDA). Subsequently, several other drugs have been approved following their trials, such as Acoramidis (another transthyretin stabilizer) and Vutrisiran (a TTR gene silencer). These drugs have proven effective; however, the choice of therapy has been based on cost, accessibility, and patient preference, which may affect management in resource-limited countries [7].

Following the different diagnostic and treatment approaches, ATTR-CA has substantial cardiovascular morbidity and mortality. Important markers for prognosis and disease progression include heart-failure hospitalization, thromboembolic events, and atrial arrhythmias, in addition to other heart events that may affect outcomes and treatment strategies. Overall, differences in demographic, socioeconomic, genetic, and healthcare-related factors have been linked with variation in ATTR-CA presentation and disease subtypes [3].

Existing evidence suggests that racial and ethnic disparities may arise across the ATTR-CA care pathway. However, findings have been inconsistent, especially for clinical outcomes, and the relationship between TTR genotype, genetic ancestry, and self-identified race and ethnicity remains complex, particularly given the higher prevalence of the pV142I variant among individuals of African ancestry [2, 8]. Also, the extent of this disparity across the treatment era and across racial and ethnic populations remains uncertain [9]. Despite emerging evidence, available evidence is fragmented across individual studies, with a focus on different aspects of the care pathway. In addition, the impact of socioeconomic and healthcare-related factors, such as care accessibility and diagnostic pathways, has not been consistently characterized [9]. Hence, the need for a focused systematic review, which intends to evaluate racial and ethnic differences in the diagnosis, management, and clinical outcomes of ATTR-CA based on available evidence. Specifically, it will examine whether race and ethnicity differ in diagnosis, disease severity, management and treatment, and clinical outcomes. It will also explore the genetic, socioeconomic, healthcare-related, and clinical factors that may contribute to or modify these differences.

## 2. Methods

## 2.1 Review Design and Reporting Guideline

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [10]. The review's protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420261404519). Because eligible studies differed substantially in exposure definitions and outcome reporting, we could not conduct a quantitative meta-analysis. The review therefore proceeded with a focused, structured narrative synthesis.

## 2.2 Search Strategy

We carried out a systematic search across six electronic databases: PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, CINAHL, ScienceDirect, and Embase. We ran the searches between June and July 2026 and retrieved 1,073 records.

Our search strategies combined controlled vocabulary and free-text terms grouped into three concept blocks: (1) transthyretin cardiac amyloidosis (for example, "transthyretin amyloidosis," "ATTR-CM," "ATTR-CA," "hereditary transthyretin amyloidosis," "wild-type transthyretin amyloidosis"); (2) race and ethnicity (for example, "race," "ethnicity," "racial disparities," "health disparities," "Black," "African American," "Hispanic"); and (3) the clinical domains central to this review (for example, "diagnosis," "management," "treatment," "clinical outcomes," "prognosis"). These blocks were combined using Boolean operators and adapted to the specific syntax of each database.

## 2.3 Eligibility Criteria

We included studies that enrolled adult patients with a confirmed diagnosis of transthyretin cardiac amyloidosis (either wild-type or hereditary), where diagnosis was established by endomyocardial biopsy or bone-avid radionuclide scintigraphy. For ATTRv, TTR genetic testing was considered supportive of genotype classification but was not accepted alone as evidence of cardiac amyloidosis. To be eligible, studies had to report data stratified by race or ethnicity on diagnosis, management, or clinical outcomes.

Eligible study designs comprised prospective or retrospective cohort studies, cross-sectional studies, and prevalence studies published as full-text, peer-reviewed articles in English. We excluded studies that did not disaggregate findings by race or ethnicity, focused only on non-cardiac amyloidosis phenotypes, or were case reports, conference abstracts, editorials, or reviews without original data.

## 2.4 Study Selection

After removing duplicates, two reviewers [MOO and OA] independently screened all titles and abstracts against our eligibility criteria, followed by a full-text assessment of potentially eligible papers. Any discrepancies between reviewers were resolved by a third reviewer [V.O.A] at both stages.

Of 1,073 records identified, 941 unique records were screened after deduplication, 78 underwent full-text review, and 9 studies met all eligibility criteria and were included in the synthesis. Study selection is summarized in a PRISMA 2020 flow diagram (Fig. 1).

## 2.5 Data Extraction

Two reviewers [MOO and OA] independently extracted data in duplicate using a standardized form, with discrepancies resolved by a third reviewer [V.O.A]. Extracted variables included study author and year, country/setting, study design, sample size, method of race/ethnicity ascertainment, ATTR-CA genotype

(variant vs. wild-type), diagnostic modality, exposures and comparators, outcomes assessed, statistical methods, and key findings.

## 2.6 Study Quality assessment

Two reviewers [M.O.O and V.O.A] independently assessed risk of bias, resolving disagreements with a third reviewer [OA]. Tools were matched to study design. The Quality in Prognosis Studies (QUIPS) tool [11] was used for the seven studies examining race or ethnicity as a prognostic factor for clinical or biomarker outcomes, across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies [12] was applied to the single site-level recruitment analysis, and the JBI Critical Appraisal Checklist for Prevalence Studies [13] was used for the single formal prevalence study.

Each domain was rated as low, low-to-moderate, moderate, moderate-to-high, or high risk of bias; “unclear” was used when insufficient reporting precluded a judgment. Intermediate ratings (for example, low-to-moderate) were assigned when a domain met some but not all criteria for the adjacent, higher-risk category. An overall per-study judgment was assigned using the same scale. Full domain-level ratings and rationale are provided in Supplementary Table 2.

## 2.7 Data Synthesis

The included studies differed considerably in how race was defined (self-identified versus EMR-derived), the effect measures used, outcome definitions, and the extent to which they adjusted for genotype and site-level confounding. As a result, no outcome met our pre-specified threshold for quantitative pooling, and we did not perform a meta-analysis.

Instead, we synthesized the findings narratively in line with the Synthesis Without Meta-analysis (SWiM) reporting guideline [14]. Results were organized by clinical domain: diagnosis, management, and clinical outcomes. For each domain, we described the direction, consistency, and magnitude of race- or ethnicity-related effects across studies, considering each study’s methodological quality and risk-of-bias profile.

# 3. Results

## 3.1 Characteristics of Included Studies

Nine studies published between 2022 and 2026 were included in this systematic review [8, 9, 15, 16, 17, 18, 19, 20, 21], comprising six multicenter studies [15, 16, 17, 18, 20, 21] and three single-center studies [8, 9, 19]. The studies assessed the clinical presentation, ATTR subtypes, diagnostics, management, and clinical outcomes. In terms of study design, seven of the included studies used a retrospective cohort design [8, 9, 15, 16, 19, 20, 21], while two studies utilized a multicenter cross-sectional design [17, 18]. Only two studies included centers outside the United States, incorporating centers from Italy and Spain [15, 16]. Two of the studies selected their cohorts from the same parent trial, SCAN-MP; multiple other studies used patients from the same centers at Columbia University [15, 16, 17, 18, 21] and Cleveland Clinic [8, 21], possibly causing overlapping patient populations. Sample sizes ranged from 62 patients in one single-center study [19] to 1350 in a multicenter study [21]. The patients enrolled were predominantly elderly, with a mean age of 76.3, with male patients accounting for approximately three-fourths of the total sample [8, 9, 15, 16, 17, 18, 19, 20, 21]. Characteristics of the included studies are summarized in Table 1.

Table 1
Overview of Included Studies

| S/N | Author & Year | Country | Study Design & Setting | Sample Size (N) | Patient Characteristics | Race/Ethnicity | ATTR Subtype | Diagnostic Method | |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Batra et al. 2022 | US/Italy | Retrospective cohort; Columbia University (NY) and Careggi University Hospital (Florence, Italy) | 70 | 53 Black, 17 White; mean age 72.3y (Black) vs 74.2y (White)<br><br>Male 60.4% vs 70.6% | Black vs White (self-identified) | Hereditary (pV142I) only, same genotype both groups | Endomyocardial/extracardiac biopsy (62.3% Black) vs 99mTc-PYP/HMDP scintigraphy (70.6% White)<br><br>P = 0.016 | |
| 2. | Mitrani et al. 2023 | US/Spain/Italy | Retrospective, 3 international centers (Columbia NY, Madrid, Bologna) | 558 | 488 White, 70 Black; age ~ 72-78y across groups; male 90% (White w/AF) vs 64% (Black w/AF) | Black vs White (self-identified) | ATTRwt / ATTRv, mixed | Endomyocardial/extracardiac biopsy or Tc99m-PYP/HMDP scintigraphy per standard criteria | |
| 3. | Shankar et al. 2024 | USA | Retrospective, single center (Johns Hopkins Hospital) | 282 (264 in race analysis) | 129 Black, 135 White; median age 74.3y vs 75.9y<br><br>Male 70.5% vs 87.4% | Black vs White (self-reported), stratified by ADI | ATTRwt 45% / ATTRv 55% (pV142I 39%) | Endomyocardial biopsy or PYP scintigraphy | |
| 4. | Khedraki et al. 2024 | USA | Retrospective, single referral center (Cleveland Clinic) | 694 | 502 White-WT, 139 Black-V122I, 53 Black-WT; age 80y/75y/81y;<br><br>Male 92%/78%/74% | White vs Black, by genotype (self-declared) | Wild-type and hereditary V122I | Endomyocardial biopsy or non-biopsy criteria (ASNC guidelines) | |
| 5. | Wardhere et al. 2024 | USA | Multicenter recruitment analysis (SCAN-MP); Columbia, Harlem Hospital, Boston Medical Center, Yale | 1,474 eligible; 560 enrolled | Enrolled cohort age ~ 70-75y;<br><br>Male 35.7%-55.1% depending on site | Self-identified Black or Caribbean Hispanic | N/A (recruitment analysis, not diagnosis-specific) | N/A | |
| 6. | Ruberg et al. 2025 | USA | Prospective multicenter screening (SCAN-MP); same 4 sites as Wardhere | 646 | 550 Black, 186 Caribbean Hispanic; median age 73y;<br><br>50.6% Women | Black vs Caribbean Hispanic (self-identified) | Of confirmed cases: 55.8% wild-type, 44.2% V142I | Tc99m-pyrophosphate scintigraphy + TTR genotyping | |
| 7. | Li et al. 2025 | USA | Retrospective, single center | 62 | 19 Black, 43 non-Black; mean age 76.7y<br><br>Male 94.7% vs 97.7% | Black vs non-Black (self-identified) | Wild-type only | Standard diagnostic criteria (not further detailed in source) | |
| 8. | Nouhossi et al. 2025 | USA | Retrospective, multicenter CMR cohort (4 academic centers, SCMR registry) | 231 | 114 Afro-Caribbean, 117 White; median age 77y<br><br>Male 71% vs 93% | Afro-Caribbean vs White (EMR-derived) | Genotype-positive 74% AC vs 18% White (95% of AC mutations = pV142I) | Cardiac MRI (T1 mapping, ECV, LGE) plus standard ATTR-CA criteria | |
| 9. | Boursiquot et al. 2026 | USA | Retrospective, multicenter biomarker cohort (Columbia + Cleveland Clinic) | 1,350 | 1,224 White, 126 Black; age 79y both groups<br><br>Male 81% vs 91% | Black vs White (self-reported) | Wild-type only | Cardiac scintigraphy with 99mTc-labeled bone-avid radiotracers | |

## 3.2 Risk of Bias and Methodological Quality of Included Studies

Risk of bias varied across the nine included studies (Table 2). Two studies, Khedraki et al. (2024) and Boursiquot et al. (2026) [8, 21], were judged to be at low-to-moderate risk of bias overall. Both addressed the central confounding threat of near-total collinearity between Black race and Val122Ile/V142I genotype through three-way race-genotype stratification and restriction to wild-type disease, respectively. Two studies, Shankar et al. (2024) and Ruberg et al. (2025) [9, 18], were judged to be at moderate risk. Four studies, Batra et al. (2022), Mitrani et al. (2023), Wardhere et al. (2024), and Nouhossi et al. (2025) [15–17, 20] were judged to be at moderate-to-high risk, primarily due to unresolved race-genotype or race-site collinearity in the confounding domain. Li et al. (2025), a research letter with an unstated race ascertainment method and a small Black subgroup (n = 19), was judged to be at high risk [19].

Across the seven QUIPS-appraised prognostic-factor studies, confounding was the most consistent source of bias. Across the two JBI-appraised studies, the principal limitation was the absence of multivariable adjustment for site-level or individual-level confounders. Full domain-level ratings and rationale are provided in Supplementary Table 2.

Table 2
Summary of Overall Quality Judgments

| S/N | Author & Year | Study Design | Tool Used | Overall Judgment |
|---|---|---|---|---|
| 1 | Batra et al. 2022 | Retrospective cohort | QUIPS | Moderate-to-High |
| 2 | Mitrani et al. 2023 | Retrospective cohort | QUIPS | Moderate-to-High |
| 3 | Shankar et al. 2024 | Retrospective cohort | QUIPS | Moderate |
| 4 | Khedraki et al. 2024 | Retrospective cohort | QUIPS | Low-to-Moderate |
| 5 | Wardhere et al. 2024 | Cross-sectional recruitment analysis | JBI (Cross-Sectional) | Moderate-to-High |
| 6 | Ruberg et al. 2025 | Prospective cross-sectional prevalence study | JBI (Prevalence) | Moderate |
| 7 | Li et al. 2025 | Retrospective cohort | QUIPS | High |
| 8 | Nouhossi et al. 2025 | Retrospective multicenter CMR cohort | QUIPS | Moderate-to-High |
| 9 | Boursiquot et al. 2026 | Retrospective multicenter biomarker cohort | QUIPS | Low-to-Moderate |

## 3.3 Race and Ethnicity of Study Populations

Race/ethnicity was established using self-reporting in eight of the studies [8, 9, 15, 16, 17, 18, 19, 21]. The remaining study implemented electronic medical record-derived race classification [20]. Racial comparison was mostly done between Black and white patients [9, 15, 16, 21]; another study compared White and Afro-Caribbean patients [20]. One study further categorized Black patients into two distinct genetic cohorts (p.V142I vs. wild-type) and compared them against white patients with a wild-type subtype [8]. The two SCAN-MP studies compared Black and Caribbean Hispanic groups [17, 18], and one other study grouped patients as Black and non-Black [19]. No study reported outcomes for other racial/ethnic groups. Across the studies, Black participants were of similar or slightly younger age than the white population and also had a larger proportion of females [8, 9, 15, 16, 19, 20, 21].

## 3.4 ATTR Subtypes and Diagnostic Methods

Among the included studies, eight reported the ATTR subtype [8, 9, 15, 16, 18, 19, 20, 21]. Of these, five studies included both hereditary/variant and wild-type [8, 9, 16, 18, 20], two studies included wild-type only [19, 21], and one study included only the hereditary type [15]. The distribution of transthyretin cardiac amyloidosis subtypes showed a complex interplay between race/ethnicity and genetic carriage. The included studies showed that the p.V142I (historically V1221) mutation was disproportionately found in patients of African descent. One study conducted at Johns Hopkins Hospital showed a concentration of this allele in Black patients at 79%, compared to 1% in the white cohort [9]. Another study reported that 74% of Afro-Caribbean patients carried this variant, compared with only 18% in white patients [20].

Other studies have challenged the traditional association of wild-type disease exclusively with white patients [8, 19]. Wild-type disease appears to be underappreciated in minority populations. A large single-center study found that 28% of the black cohort had wild-type disease [8]. Another study also showed that 30% of patients with wild-type disease identified as Black [19]. This is further supported by the multicenter SCAN-MP screening trial of older Black and Caribbean Hispanic heart failure patients, which revealed that 55.8% of cases had wild-type disease [18].

The studies used different diagnostic modalities, ranging from non-invasive methods, such as TTR genotyping and bone scintigraphy, to invasive cardiac or extracardiac biopsy with typical imaging findings. Black patients were more likely to be diagnosed using invasive modalities compared with white patients (62.3% vs 17.7%), while white patients were mostly diagnosed via non-invasive bone scintigraphy (70.6%; p = 0.016) [15]. Another study observed that Black patients were less likely to undergo scintigraphy for diagnosis compared with white patients (33% vs. 48%; p = 0.012) [9].

## 3.5 Management and Treatment Patterns

The management of diagnosed patients across these nine studies included conventional heart failure pharmacotherapy, AF and anticoagulation therapy, disease-modifying therapies, invasive devices, and surgical interventions.

Disease-modifying treatment was reported in four of the included studies [8, 9, 19, 20], but showed a mixed picture. One study comparing wild-type cohorts showed that rates of disease-modifying therapy prescription were significantly lower in black patients with ATTRwt-CA compared with non-Black wild-type

patients (68.4% vs 88.4%) [19]. Similarly, a multicenter study of patients undergoing cardiac magnetic resonance showed that Afro-Caribbean patients were less likely to receive ATTR therapy compared with white patients (68% vs 95%) [20]. Conversely, two single-center studies reported no statistically significant differences in Tafamidis prescription rates by race (35% vs 42%; 8.7% vs 10.6%;) [8, 9]. The use of gene-silencer drugs, Patisiran or Inotersen, was reported in one study, which showed their clinical use was mainly in the hereditary Black VV122Lvariant cohorts (8.2%) compared with 0.4% in white-WT and 0% of Black-WT patients [8].

Anticoagulation management for atrial fibrillation also differed among groups. Compared with white patients, Black patients were less often on anticoagulation (5% vs 18%) and had more labile INR (time in therapeutic range < 60%) values while on Warfarin (91% vs 20%) [16].

Conventional heart failure management using neurohormonal blockade showed no major difference in overall prescription patterns between Black and white cohorts [15]. The usage patterns of loop diuretics showed that Black patients were more likely to be on diuretics at presentation compared with white cohorts (81.7% vs. 60%) [9]. In a multicenter study, Black wild-type patients required a higher weight-adjusted daily loop diuretic dose (0.3 mg/kg/day) compared to 0.2 mg/kg/day for white patients [21].

## 3.6 Clinical outcomes by race and ethnicity

Clinical outcomes monitored varied across the studies, including mortality, hospitalization, thromboembolism, and biomarkers. The studies revealed that Black and Afro-Caribbean groups experienced significantly poorer outcomes. A multicenter study showed that mortality was significantly higher in black patients with ATTR-CA and AF compared with white patients [16]. In a retrospective cohort at Johns Hopkins Hospital, Black race was associated with a nearly 2-fold independent hazard of heart failure hospitalization or death over five years of follow-up (adjusted HR: 1.97; P = 0.007); however, when restricted to death alone, black patients were not at a statistically significant risk [9]. Another single-center study demonstrated that Black race was independently associated with a higher risk of long-term mortality (adjusted HR: 4.85; P = 0.007) [19]. Similarly, a study of patients undergoing CMR reported that Afro-Caribbean race was independently associated with a 1.68-fold (p = 0.02) increased hazard of the primary composite endpoints (HF hospitalization or mortality) [20]. Conversely, one study reported no statistically significant difference between Black and white patients regarding clinical outcomes [15]. Another study showed that the difference in survival between black patients and white-WT patients was no longer statistically significant in the Tafamidis era [8].

Thromboembolic events associated with AF were higher among black patients despite a lower prevalence of AF compared with white patients (adjusted HR: 5.78; P < 0.001) [16]. In a large cohort of patients with wild-type disease, black patients had a significantly higher unadjusted baseline N-terminal pro-B-type Natriuretic Peptide (NT-proBNP), but this difference was no longer statistically significant after adjustment for disease severity [21]. These differences in mortality, hospitalization, biomarkers, and thromboembolic risk across racial and ethnic groups are summarized in Fig. 2.

## 3.7 Main Findings Across Racial and Ethnic Groups

Differences were identified across several domains, including racial and ethnic characteristics, TTR genotype, diagnostic approach, management, and clinical outcomes. Across the included studies, Black and Afro-Caribbean patients often presented with more advanced disease. These findings were noticed in both wild-type and hereditary ATTR-CM cohorts [9, 15], and were supported by higher prior heart failure hospitalization [9], worse renal function [15, 19], higher baseline NT-proBNP (median NT-proBNP: 2,529 vs 1,905 pg/mL, P = 0.03) [21], and lower biventricular ejection fraction [20].

Historically, wild-type disease (ATTRwt-CA) has been thought to be exclusive to older white men. The results of these studies challenge this notion. One study showed that 28% of black ATTR-CA patients had wild-type disease [8]. Similarly, in the SCAN-MP screening trial, 55.8% of diagnosed Black and Caribbean Hispanic subjects had wild-type disease [18]. This demonstrates that genotype-based screening for Black patients may be inadequate. The hereditary variant was found mainly in Black patients [16]. This phenotype was associated with more advanced disease at diagnosis and carried a higher hazard of events [8].

The studies have shown significant disparities in diagnosis and management between Black and white cohorts. Black patients were significantly more likely to undergo invasive modalities for diagnosis and less likely to be diagnosed through non-invasive scintigraphy [9, 15]. In terms of treatment, Black patients were less likely to receive targeted therapy [19, 20]. In another study assessing the management of AF, Black patients were more likely to receive no treatment and were more likely to have labile INR [16].

These issues culminate in Black and Afro-Caribbean patients experiencing statistically significant rates of composite events [9, 16, 19, 20]. However, these outcomes might not be solely due to biological differences between racial groups. Socioeconomic conditions may also influence survival. Black patients have more exposure to neighborhood deprivation (ADI category 3: 66% vs 28%, P = 0.004). In patients residing in deprived areas (ADI > 25), Black patients faced a 2.77-fold higher hazard of hospitalization or mortality than white patients. In contrast, there was no difference in survival between racial groups in wealthier neighborhoods [9]. The effect of socioeconomic conditions and access to appropriate healthcare is further supported by the lack of disparity in access to therapy in the studies conducted at single referral centers at Johns Hopkins and Columbia University [8, 9].

These findings suggest that structural barriers to healthcare, screening biases, and socioeconomic factors may contribute to poorer outcomes. This is supported by the fact that survival discrepancies between Black and white patients were eliminated in contemporary cohorts (2018–2021) enrolled in an amyloidosis management program where equal access to disease-modifying therapies was established [8].

# 4. Discussion

## 4.1 Summary of Main Findings

This review synthesized evidence from 9 studies and examined racial and ethnic differences in the diagnosis, management, and clinical outcomes of transthyretin cardiac amyloidosis. Collectively, the findings showed disparities between Black and White patients across several domains of care [8, 9, 15–21]. Studies reported more advanced disease, greater morbidity, and worse survival among Black patients when compared with white patients [8, 15, 20]. While the p.V142I TTR variant was highly prevalent among black patients, its phenotypic penetrance was incomplete at 39%, and a substantial proportion of ATTR-CM cases in the black population were wild type, emphasizing that genotype is insufficient for diagnosis [18, 22]. Racial differences extend to diagnostic biomarkers, treatment access, and clinical outcomes, with black patients exhibiting higher levels of NT-proBNP, lower uptake of the disease-modifying therapies and an increased risk of heart failure hospitalization and mortality [9, 19, 21]. These disparities were also associated with social deprivation, with neighborhood-level socioeconomic disadvantage independently predicting advanced disease stage and worse survival [9, 23].

## 4.2 Differences in ATTR Subtypes and Genetic Variants

A defining feature of ATTR-CM is the different distribution of TTR genotypes across populations with different ancestral backgrounds. The p.V142I (V122I) variant is present in about 3.4% of self-identified black individuals in the United States. The p.V142I variant is more common among individuals of African ancestry and is an important genetic cause of hereditary ATTR-CM [22, 24]. In the REGARDS cohort, p.V142I carriers had a higher incident risk of heart failure of 2.43-fold and a 4.19-fold higher risk of mortality from heart failure compared to non-carriers, which emphasizes the clinical significance of these variants [24]. Similarly, in the study by Jackson Heart Study, p.V142I carriers had an 80% higher risk of incident heart failure and a greater burden of chronic myocardial injury over time, though no evidence of adverse cardiac remodeling in midlife [25].

However, the relationship between genotype and clinical disease is not straightforward. The SCAN-MP study demonstrated that among older black individuals with heart failure and increased wall thickness, the phenotypic penetrance of p.V142I was only 39% overall, which increased to 63% among those aged 75 years and older [22]. Moreover, the majority of ATTR-CM cases identified in black participants were wild type, which indicates that a genotype-first screening approach would miss a substantial proportion of affected individuals [18, 22]. This incomplete penetrance emphasizes the importance of clinical phenotyping alongside genetic testing. Genomic screening programs have demonstrated feasibility in identifying individuals at risk, with over half of individuals with positive p.V142I having at least one hATTR-related systemic feature at the time of the result disclosure [26]. Nevertheless, the presence of wild-type ATTR-CM among Black patients who experienced similarly poor outcomes to their White counterparts with wild-type disease suggests that the observed racial differences cannot be explained by TTR genotype alone [8].

## 4.3 Difference in Diagnosis, Management, and Treatment

Racial differences were consistently observed across diagnostic, management and treatment domains. Black patients with ATTR-CM presented with more advanced disease at diagnosis, evidenced by the higher levels of NT-proBNP, which is a key marker of disease severity, although this difference was attenuated after adjustment for clinical characteristics, which suggests that the observed difference in NT-proBNP may be related to differences in disease severity and other clinical characteristics rather than race itself [21]. Diagnostic delays were compounded by socioeconomic deprivation, with patients from high social Deprivation index areas having twice the odds of presenting with advanced Columbia stage at their first visit [23]. Shankar et al. (2024) also demonstrated that black patients with area deprivation index > 25 had a 2.77-fold increased risk of heart failure hospitalization or death, independent of disease stage, which suggests that neighborhood-level disadvantage may contribute to differences in diagnosis and clinical outcomes [9].

Access to treatment also differed by race and socioeconomic status. Black patients with wild-type ATTR-CM had lower utilization of disease-modifying therapy when compared with non-Black patients, which may partly explain the higher adjusted mortality observed [19]. However, in the tafamidis era, Khedraki et al. (2024) found that the survival disparity between black and white patients lost statistical significance after adjusting for treatment exposure, which suggests that equitable access to therapy may mitigate outcome differences [8]. Despite this, significant barriers to access to treatment still persist. Miller et al. (2024) revealed a median 65-day delay from diagnosis to tafamidis receipt, with patients from lower-income neighborhoods experiencing delays nearly twice as long as those from higher-income areas. These delays, compounded by the financial complexity of medication approval, disproportionately affected patients with lower socioeconomic status [27].

Furthermore, disparities extended to anticoagulation management. Mitrani et al (2023) found that despite lower atrial fibrillation prevalence, black people with ATTR-CM and atrial fibrillation had a thromboembolic risk about 5.78-fold higher, which may be partly related to less frequent anticoagulation and more labile INR among those on warfarin. Collectively, the findings indicate that black patients face multilevel barriers, which range from delayed diagnosis to inequitable access to treatment and suboptimal management of complications, which may contribute to worse clinical outcomes [16].

## 4.4 Difference in Clinical Outcomes

Clinical outcomes consistently favored white patients across multiple studies. Black patients experienced a higher rate of heart failure hospitalization, thromboembolic complications and mortality compared to the white population. In the multicenter CMR cohort, Afro-Caribbean race was independently associated with the composite outcome of death or heart failure hospitalization after adjustment for genotype and CMR parameters. However, the factors underlying this association remain unclear [20]. Shankar et al. (2024) also revealed that black patients with an area deprivation index > 25 had a 2.77-fold higher risk of heart failure hospitalization or death, independent of National Amyloidosis Centre stage, which indicates that social disadvantage amplifies outcome disparities beyond disease severity [9].

Mortality differences were particularly pronounced in wild-type ATTR-CM. Li et al. (2025) revealed that black patients with wild-type disease had significantly higher adjusted mortality when compared with non-black patients, despite having similar age and sex distribution [19]. However, Khedraki et al. (2024) reported that the survival disparity between Black p.V142I carriers and White wild-type patients was no longer statistically significant in the tafamidis era. Because these groups differed in both race and TTR group, this finding does not allow the independent role of genotype, race, or treatment exposure to be determined [8]. Thromboembolic risk also differed substantially, as Mitrani et al. (2023) found that despite lower prevalence of atrial fibrillation, black patients with AF had a 5.78-fold higher thromboembolic risk, which may be partly related to differences in anticoagulation management [16]. Notably, Batra

et al. (2022) found that there was no significant difference in mortality between black and white patients with identical p.V142I genotypes, which suggests that when genetic and treatment factors are comparable, outcomes may converge [15].

## 4.5 Factors Contributing to Observed Differences

The observed disparities in ATTR-CM may reflect a complex interplay of genetic, socioeconomic, clinical, and healthcare-related factors. Genetically, the p.V142I variant is associated with increased risk for heart failure, but its incomplete penetrance indicates that genotype alone does not determine clinical outcomes, as suggested by 39% overall in the SCAN-MP cohort [22, 24]. Environmental and social factors may also contribute to differences in clinical risk. Besides, social deprivation emerged as a powerful predictor of outcomes across multiple studies. Fahed et al. (2025) demonstrated that a high social deprivation index was associated with twice the odds of advanced Columbia stage at presentation, with poverty and lack of vehicle access as the most significant subcomponents [23]. Similarly, it was found that neighborhood-level disadvantage, measured by area deprivation index, independently predicted heart failure hospitalization or death in black patients, even after accounting for disease stage.

The observed disparities may also be further compounded by differences in access to quality healthcare. Patients from lower-income areas experienced significantly longer delays to tafamidis receipt, while Wardhere et al. (2024) identified that direct recruitment by primary cardiovascular care teams was the strongest predictor of research enrollment among the underrepresented minorities, which suggests that engagement with clinical care pathways is critical [17, 27]. Additionally, differential management of complications, such as suboptimal anticoagulation in black patients with atrial fibrillation, may contribute to differences in outcomes [16]. Spencer-Bonilla et al. (2021) emphasized that these structural barriers, combined with underrepresentation in clinical trials and limited treatment accessibility, may contribute to persistent disparities beyond genetic risk [28]

## 4.6 Comparison with Previous Evidence

The findings of this study align with and also extend the broader study on racial disparities in cardiovascular disease. Spencer-Bonilla et al. (2021) previously highlighted that ATTR-CM disproportionately affects older adults and people of African descent, yet most clinical data originated from North American and European populations, with black patients being underrepresented in clinical trials [28]. Our review reinforces this and shows evidence of diagnostic delays and differences in treatment access despite the high prevalence of p.V142I in Black populations [23, 27]. The incomplete penetrance of p.V142I observed in the SCAN-MP cohort aligns with the findings from population-based studies and shows that genotype alone does not fully explain heart failure risk [22, 24, 25]. Furthermore, the association between social deprivation and adverse outcomes in ATTR-CM parallels well-established disparities in heart failure outcomes more broadly, where neighborhood-level factors independently predict prognosis [28]. Our review extends this evidence by specifically quantifying the magnitude of disparities across diagnosis to treatment in ATTR-CM.

## 4.7 Clinical and Research Implications

These findings carry important implications for clinical practice and future research. Clinically, clinicians should maintain a high index of suspicion for ATTR-CM in black patients who present with heart failure and increased wall thickness, recognizing that wild-type disease is common, and genotype-only approaches may miss patients with ATTRwt-CA and should not replace appropriate clinical and phenotypic assessment [18, 22]. Equitable access to disease-modifying therapies must be prioritized, given that treatment delays are longest among patients from lower-income areas [27]. Research efforts should focus on enrolling diverse populations in clinical trials and evaluating screening strategies that incorporate both genetic and social risk factors. Future studies must also examine the effectiveness of multidisciplinary care models in reducing disparities.

## 4.8 Strengths and Limitations

This review considers differences in genotype, disease severity, diagnosis, treatment, and clinical outcomes in ATTR-CM while addressing an important and understudied question on racial and ethnic disparities. Some included studies may have used overlapping patient populations or data from the same clinical centers. The potential influence of socioeconomic factors and healthcare access is also explored while highlighting important gaps in the current evidence. These findings provide practical recommendations for earlier diagnosis, equitable treatment access, and future research, especially in underrepresented populations. However, there may have been overlap in patient populations across the included studies, meaning that some patients being represented in more than one study could affect the overall interpretation of the findings. Also, a quantitative synthesis could not be achieved because the studies reported outcomes using different definitions, measures, and follow-up periods. We considered the treatment outcomes, mortality, disease severity, and diagnostic and treatment measures for pooling, but the significant methodological and clinical heterogeneity across the studies made a reliable quantitative comparison inappropriate. Limiting the review to English-language, full-text articles may have excluded relevant studies published in non-English languages and introduced some biases. Including only nine studies, of which most were retrospective and conducted in the U.S., may limit the generalizability of the findings to other populations and settings.

# 5. Future Directions and Recommendations

Findings across the studies suggest that key distinguishing features may exist in the diagnosis, management, and outcomes of ATTR-CA across races and ethnic groups. Prospective multicenter studies are needed to validate these findings using standardized definitions of race and ethnicity and consistent measures. To strengthen the generalizability of findings, future studies should prioritize equitable recruitment of underrepresented racial and ethnic groups, including populations outside America. The factors responsible for diagnostic delay, including treatment access, referral patterns, socioeconomic disadvantage, and access to specialist diagnostic services, should be explored in future studies. Since many patients are often hesitant to present for care, barriers to early diagnosis are an area for researchers to explore.

Future studies should assess whether outcomes of ATTR-CA differ after equivalent access to appropriate treatment and should examine the effects of treatment delay and socioeconomic factors. This may help clarify whether observed differences in outcomes are related to treatment access or other clinical

and socioeconomic factors. Finally, patterns of racial, ethnic, and genetic ancestry reporting are particularly important in future research because the distribution of TTR variants differs across ancestral populations. ATTRv subtype is more common among individuals of African ancestry, and ATTRwt are commoner among older White individuals [29, 30]. For example, 'non-Black' cannot be assumed to be equivalent to White individuals, and 'Hispanics' should not be generalized to mean the Black race.

## 6. Conclusion

This review shows that racial and ethnic differences are present in ATTR-CM, from diagnosis and treatment through to patient outcomes. The p.V142I variant was more prevalent among Black patients, consistent with its higher frequency in populations of African descent. Several studies found that Black and Afro-Caribbean patients presented with more advanced disease and had worse outcomes compared with White patients. There were differences in the investigations used and access to disease-modifying treatment. Importantly, genetic factors alone do not appear to explain these differences, as social deprivation and access to healthcare may also contribute.

These findings highlight the importance of recognizing ATTR-CM across different racial and ethnic groups, particularly where diagnosis may be delayed. Improving awareness and access to appropriate investigations and treatment may help reduce differences in outcomes. Further studies involving more diverse populations would help clarify how genetics, socioeconomic factors and access to healthcare contribute to these differences.

## Abbreviations

ADI: Area Deprivation Index

ATTR: Transthyretin Amyloid

ATTR-CA: Transthyretin Amyloid Cardiac Amyloidosis

ATTR-CM: Transthyretin Amyloid Cardiomyopathy

ATTRv: Variant Transthyretin Amyloidosis

ATTRwt: Wild-Type Transthyretin Amyloidosis

CA: Cardiac Amyloidosis

EMB: Endomyocardial biopsy

FDA: Food and Drug Administration

MD(c): Doctor of Medicine Candidate

NT-proBNP: N-terminal pro-B-type Natriuretic Peptide

## Declarations

Acknowledgements: None

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Clinical trial number: Not applicable

Availability of data and materials: Data sharing does not apply to this article as no datasets were generated or analysed during the current study.

Competing interests: The authors declare that they have no competing interests

Funding: The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Code availability: Not Applicable

Author Contributions

OA and VOA conceived and designed the study. RSM and MOO performed the data analysis. VOA, DAW, MOO, SOO, FGO, BPO, SAA, HA, ME, RSM, and HKA contributed to drafting the initial manuscript, critically revised subsequent versions, and approved the final version for publication.

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## Figures

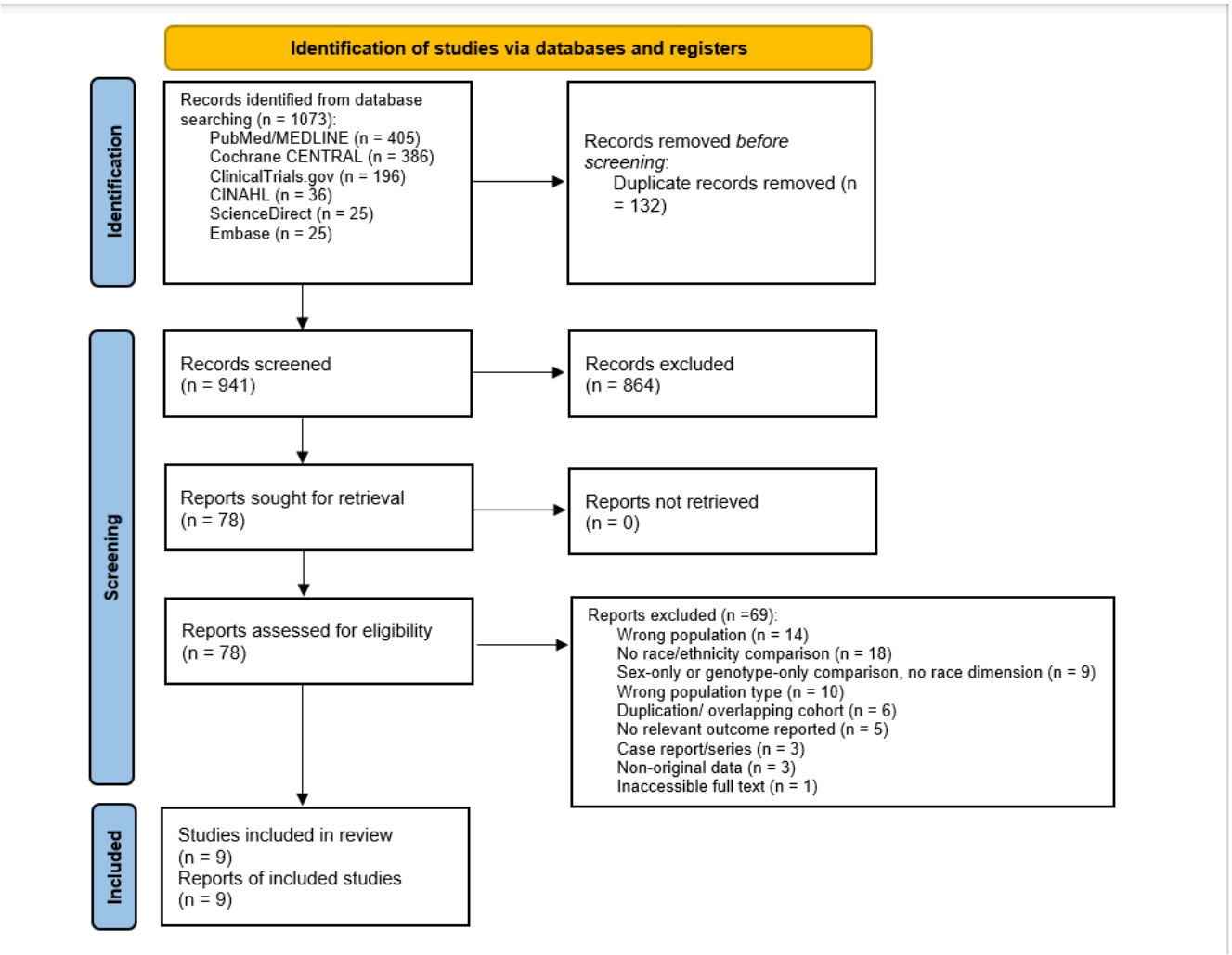



**Figure 1**

**Overview of Selection Process**

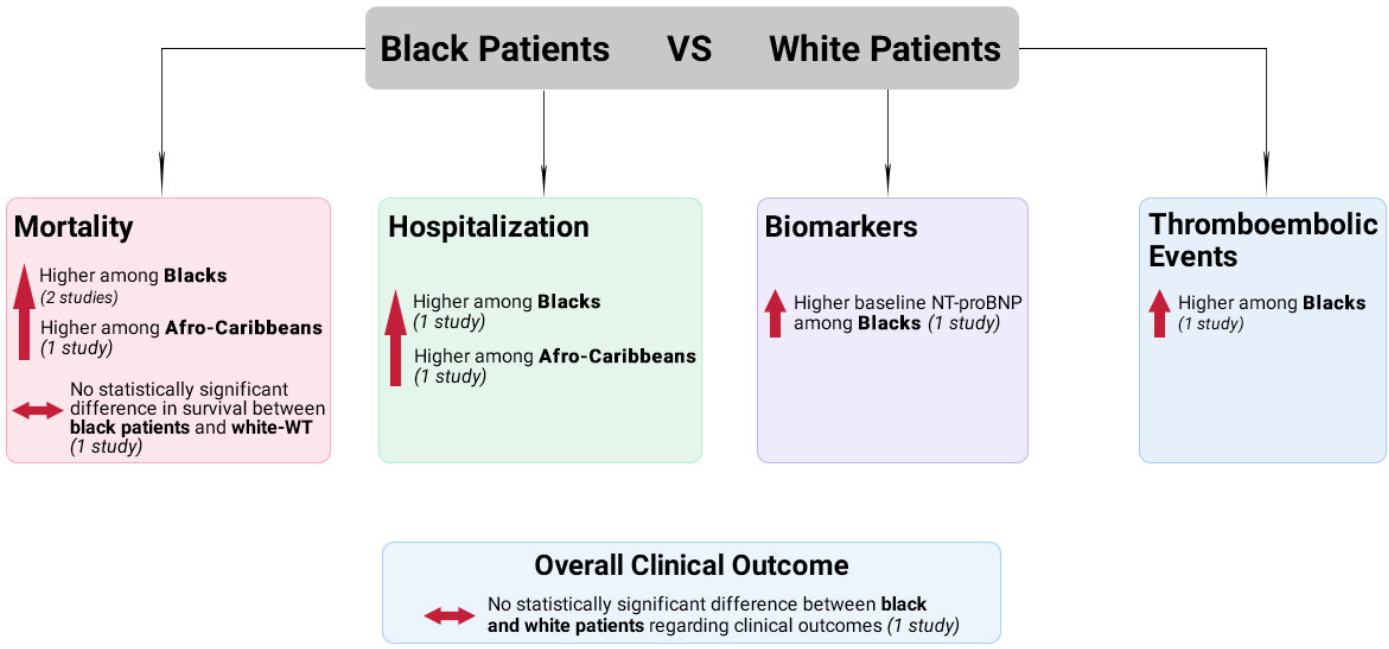



**Figure 2**

**Summary of Clinical Outcomes**

## Supplementary Files

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- QualityAppraisalSupplementaryTable.docx