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Time to Surgical Referral in Non-Hispanic White and Black Patients with Primary Hyperparathyroidism

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TIME TO SURGICAL REFERRAL IN NON-HISPANIC WHITE AND BLACK PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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Abstract

Primary hyperparathyroidism is the excessive secretion of parathyroid hormone by one or more parathyroid glands, resulting in hypercalcemia. Primary hyperparathyroidism can be safely cured by parathyroidectomy, but there are well-established racial differences in disease burden at the time of parathyroidectomy with Black patients exhibiting greater serum calcium, parathyroid hormone levels and parathyroid gland size compared to non-Hispanic White patients.

However, few studies investigate what factors contribute to these differences.

We hypothesize that Black patients experience greater time between presentation with hypercalcemia and surgical referral date than non-Hispanic White patients.

To test this hypothesis, we will carry out a retrospective review on all Black and non-Hispanic White patients in the Yale-New Haven Health System with hypercalcemia from January 2014 – December 2015.

This study may offer some insight into the racially disparate disease burden in Black patients and may suggest potential interventions to minimize racial disparities in the management of primary hyperparathyroidism.

Table of Contents

List of Tables

Chapter 1 – Introduction

Background

Racial disparities are ubiquitous in healthcare and widely cited as contributing to serious health consequences. Surgical specialties have reported disparities in disease presentation, management, and outcomes with delays in diagnosis, inconsistencies in management and disparities in access to care possibly leading to worse outcomes in Black patients.[1-5] Primary hyperparathyroidism (PHPT) is no exception as multiple studies have reported that Black patients present for curative surgery with higher disease burden than non-Hispanic White patients.[6,7]

PHPT, the most common cause of hypercalcemia, is caused by excessive secretion of parathyroid hormone (PTH) by one or more parathyroid glands and typically presents with high serum calcium levels on routine bloodwork. Diagnosis requires detection of inappropriately elevated PTH in the presence of hypercalcemia. PHPT is relatively common, with prevalence in the general population approximately 0.86%.[8] Incidence of PHPT is highest among Black patients, particularly Black women.[9]

Primary hyperparathyroidism can cause significant disease sequelae and end-organ damage such as chronic kidney disease (CKD), nephrolithiasis, and significant bone density loss.[10] Non-specific but more common symptoms include fatigue, general malaise, irritability, depression, and memory problems.[10-12] The definitive management of PHPT is surgical parathyroidectomy. It is 95-99% curative[10] and offers the most cost-effective strategy and highest quality of life compared to observation or pharmacologic therapy.[13] Consensus guidelines from the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism recommend surgery for patients who meet any one of the following criteria: < 50 years of age at the time of

presentation, serum calcium > 1 mg/dL the upper limit of normal, 24-hr urine calcium > 400 mg/dL, creatinine clearance (CrCl) < 60 mL/min, or evidence of nephrolithiasis, nephrocalcinosis, osteoporosis, or vertebral fractures.[14] Many studies criticize these guidelines as too restrictive as they fail to account for non-specific symptoms also associated with the disorder.[11,15,16] The American Association of Endocrine Surgeons (AAES) guidelines are less restrictive and recommend surgery for neurocognitive and/or neuropsychiatric symptoms as well as consideration of surgery in patients with cardiovascular disease, muscle weakness, abnormal sleep patterns, gastroesophageal reflux, or fibromyalgia.[10]

Traditionally the term "asymptomatic" PHPT refers to patients without evidence of end-organ damage such as nephrolithiasis, kidney disease, or osteoporosis. It is clear that patients who present with these classic disease manifestations benefit from surgery as surgery reduces the burden of nephrolithiasis and improves bone density and kidney function.[10,17] However, when non-specific symptoms are considered, less than 5% of patients with PHPT are truly asymptomatic, and many studies suggest that these patients would also benefit from surgery by improving quality of life,[18-20] reducing nonspecific symptoms[11,12,21] and preventing renal and skeletal complications.[16,19,20,22] A literary review by Coker et al. identified seven well-designed prospective studies that demonstrate improvement in quality of life across multiple domains following parathyroidectomy including those who had only subtle, non-classic symptoms of the disorder.[18] Recently, studies examining cardiovascular risk in hyperparathyroidism have found that patients with mild PHPT have a significantly increased risk of developing

cardiovascular disease, cerebrovascular disease, hypertension, and have higher mortality.[15,18,23-26]

Despite numerous studies demonstrating most patients with PHPT may benefit from parathyroidectomy and should, at the very least, be referred to a surgeon to discuss risks and benefits of the procedure,[16] studies have shown there is often a significant delay between diagnosis and surgery.[27-30] Even with ample evidence of racial disparities in PHPT, only one study has examined the impact of race on treatment delays.[6,7]

Multiple studies have demonstrated that Black patients present for parathyroidectomy with greater disease burden than non-Hispanic White patients. Black patients exhibit higher serum calcium levels, higher intact PTH levels, higher adenoma weight and a greater probability of double adenomas.[6,7] It is unknown why Black patients present with more severe disease at the time of surgery than non-Hispanic White patients. However, there is extensive evidence that Black patients are at risk for delayed diagnosis, referral, and treatment across medical specialties.[1,5,31,32] The solitary prior retrospective study examining racial disparities in treatment delays in PHPT found that Black patients experience a significantly longer time from first known hypercalcemia to parathyroidectomy compared to non-Hispanic White patients.[30] This study used parathyroidectomy date as a proxy for referral date which introduces confounders unrelated to appropriate management and diagnosis of the disease such as patient and provider schedules. Our study aims to eliminate those possible confounders by evaluating time to surgical referral. Nonetheless, this previous study is important in demonstrating that a delay in surgical referral could contribute to higher disease burden in Black patients.

Because there are clear consensus guidelines for surgical referral, it is important to evaluate disease presentation as a possible explanation for differences in time to referral. Black patients in the general population experience some amount of protection against many of the disease sequelae that are evaluated to determine appropriateness of surgical referral for parathyroidectomy. It is well documented that the incidence of osteoporosis and associated clinical fractures is lower in Black women than non-Hispanic White women, seemingly due to increased bone mineral density before menopause and slower rates of loss post-menopause.[33,34] Other studies have shown evidence that Black patients secrete less calcium in their urine than other races, potentially reducing the incidence of nephrocalcinosis and nephrolithiasis as well.[6,35] Few studies examine racial differences in disease presentation and questions remain about whether variations in presentation may explain longer wait times for referral and treatment for Black patients. Even if it is discovered that Black patients exhibit end-organ damage less frequently than non-Hispanic White patients with PHPT, there are no studies that suggest Black patients experience non-specific symptoms less frequently. These non-classical manifestations of the disease, as demonstrated above, can also significantly affect morbidity and quality of life. It is important to evaluate racial disparities in disease presentation to ensure surgical guidelines are appropriately identifying all patients who would benefit from surgery regardless of race.

Statement of the Problem

Black patients experience more delays in care and present with higher disease burden across medical specialties.[1-5] Studies show that PHPT incidence is highest among Black patients[8] and that Black patients are presenting for curative surgery with more severe disease than non-Hispanic White patients which may be due, in part, to delays in

care.[6,7] Delays in PHPT management result in higher morbidity, lower quality of life, and higher healthcare costs.[12,13,17,36,37] Prior studies have indicated that Black patients with PHPT experience a delay from diagnosis to surgery, but additional research is required to understand if a delay to surgical management is caused by failure of the diagnosing physician to appropriately refer Black patients for treatment or if the delay occurs after surgical referral.[30] Analysis of differences in disease presentation and fulfillment of consensus surgical criterion may help elucidate whether PHPT in Black patients is being appropriately recognized.

Goals and Objectives

The objective of the study is to determine if Black patients eligible for surgical referral for parathyroidectomy experience significantly longer time from hypercalcemia to referral compared to non-Hispanic White patients. Secondarily, we aim to characterize disease presentation among non-Hispanic White and Black patients and analyze differences in presentation that may be contributing to disparities in time to referral.

The goal is to examine one possible contributor to higher disease burden in Black patients with PHPT and to further characterize racial disparities that may potentially be addressed to improve management of primary hyperparathyroidism.

Hypothesis

Black patients at risk for surgical referral for parathyroidectomy between the years 2014 and 2015 will have a statistically significant delay in time from known hypercalcemia to surgical referral for parathyroidectomy compared to non-Hispanic White patients over a four-year follow-up period.

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Chapter 2 – Review of the Literature

Introduction

To evaluate time course from hypercalcemia to referral for parathyroidectomy among non-Hispanic White patients and Black patients with PHPT, a systematic review of the literature was performed between December 2021 and May 2022. Databases PubMed, Cochrane Library and Scopus were used. Initial MeSH terms included: *primary hyperparathyroidism, Black, parathyroidectomy* and *referral and consultation.* Alternative MeSH terms for primary hyperparathyroidism included *endocrine disorders, hypercalcemia*, and *parathyroid hormone*. Alternative MeSH terms for Black were *African American, racial groups, healthcare disparities, health status disparities,* and *health services accessibility*. Alternative MeSH terms for *referral* and *consultation included time-to-treatment,* and *delayed diagnosis.* Alternative MeSH terms for parathyroidectomy included *endocrine surgical procedures.* Other key search terms included *hypercalciuria, nephrolithiasis, osteoporosis, fragility fracture, vitamin D,* and *glomerular filtration rate.* Studies included clinical studies, systematic reviews, and meta-analyses. The relevance of articles was determined and analyzed for inclusion in the literature review. Additional references and MeSH terms were selected from previously analyzed articles as appropriate.

Participant groups throughout the paper will be referred to as Black or non-Hispanic White to be in-line with the most recent guidelines on reporting race and ethnicity in medical and science journals.[1]

Review of Empirical Studies About the Relationship Being Studied

Higher Disease Burden in Black Patients with PHPT

Multiple studies have shown that Black patients with PHPT present for parathyroidectomy with higher disease burden than non-Hispanic White patients. One

retrospective study found that Black patients presented with significantly higher median calcium (11.36[SD= 0.91] vs 11.06[SD= 0.72]mg/dL, P < .001), intact PTH (138.5[SD= 166.03] vs 117[73.22] pg/mL, P < .01), greater gland weight (P < .001), and a higher probability of double adenomas (OR= 2.83, 95% [CI], 1.36–5.88) compared to non-Black patients. Race was not necessarily self-reported in this study as it was identified via a Johns Hopkins database. Also, the comparison group included multiple non-Black races including non-Hispanic White, Asian and 19 others. The number of Asian and "other" race participants was not high enough for meaningful statistical analysis. The study also did not assess for several confounding variables, such as insurance or income, that may impact access to timely care and consequently disease severity at presentation.[2]

Another retrospective study assessed racial disparities among 2,393 self-identified Black and non-Hispanic White patients who underwent parathyroidectomy between 1997 and 2015. The study found that Black patients had higher preoperative calcium (10.9 vs.10.8 mg/dl, $p < 0.001$) and PTH levels (122 vs. 97 pg/ml, $p < 0.001$) as well as larger glands by size (1.7 vs. 1.5 cm, $p < 0.001$) and mass (573 vs. 364 mg, $p < 0.001$). On multivariate analysis, after controlling for preoperative calcium and PTH, Black race and lower median income remained significantly associated with higher gland weight and size. This study did not find any difference in rate of double adenomas or multi-gland hyperplasia between the two groups.[3] Both of these prior studies only included patients who eventually underwent parathyroidectomy which selects for patients with more severe disease. However, we expect the population of patients who eventually undergo parathyroidectomy to be similar to the population who is referred for surgical evaluation.

Neither study was designed to assess disease duration which could impact the severity of disease at presentation for surgery.[4,5]

Delay in Diagnosis and Treatment for Black Patients Across Medical Specialties

Delay in diagnosis and treatment for Black patients has been well documented across medical specialties. Black women experience disproportionately longer delays in diagnosis and treatment of breast carcinoma.[6] Black patients are also more likely to present with later stage colorectal cancer[7,8] and are less likely to receive timely and appropriate treatment in NSCLC.[9] Similarly, time-to-treatment is significantly longer for Black patients with diabetic eye disease than for non-Hispanic White patients.[10]

This has also been studied within endocrinology, particularly in benign and malignant thyroid disorders. Kuo et al. reviewed EHR data for 1,189 patients receiving a thyroidectomy for benign thyroid disease to examine the association between race, referral patterns and disease severity. Only patients who self-identified as Black or non-Hispanic White were included. The primary outcome of the study was time from first presentation to a physician for the thyroid condition to surgical referral. The study found that Black patients had more severe disease as evidenced by a greater percentage reporting compressive symptoms (45% vs. 21.2%, $p < .01$) and dysphagia (19% vs. 10.1%, $p < .01$) and by greater median specimen mass at time of surgery (71 g, IQR 33.5-155.3 vs. 24.3 g, IQR 15.0-50.2, $p < .01$). Black patients also experienced a longer median time in years from diagnosis to surgical evaluation with a median time of 1 year (IQR 0-5) compared to 0 years (IQR 0-2) for non-Hispanic White patients ($p < .01$) even after adjusting for median income quartile. It has been established in a number of studies that Black patients present with more severe thyroid and parathyroid disease.[2,3,11-13] However, this study offers one possible explanation by demonstrating that Black patients

experience longer delays to referral for treatment than non-Hispanic White patients. There is a clear role for examining racial disparities in time to referral within PHPT and whether referral delays may be contributing to more severe disease in Black patients.

Delay in Diagnosis and Treatment in Primary Hyperparathyroidism

Two retrospective cohort studies have examined diagnosis and treatment delays in PHPT. However, only one study evaluated the association between race and time from diagnosis to surgical treatment.

Naples et al. examined whether patients who met at least one consensus surgical criterion resulted in a faster time course from hypercalcemia to PTH obtainment, from PTH obtainment to diagnosis of PHPT via ICD-9 code in the patient's chart and from diagnosis date to surgery date. Study groups were determined based on whether patients met at least one criterion from the 2008 surgical guidelines as well as additional criterion from the 2013 guidelines. The study found that the time course to each end-point was similar between patients that met at least one objective criterion and those that did not. The overall mean time course for patients who met at least one criterion was 3.9 ± 0.3 years ($P = .87$) whereas the overall time course for patients who did not meet criteria was 3.8 ± 0.5 years. The study also analyzed the impact of each individual surgical criterion. Age and calcium values had the greatest impact on time to surgery. Patients less than 50 years-old underwent surgery earlier (2.3 ± 0.7 vs 4.1 ± 0.3 years, $P=.01$) as did patients with calcium > 11.5 mg/dL (2.3 ± 0.7 vs 4.1 ± 0.3 years $P = .03$). Osteoporosis, nephrolithiasis, estimated glomerular filtration rate (eGFR) and 24-hr urine calcium did not have an impact on time course.[14] This study is important because it provides an approximation of how long patients with PHPT wait for surgery after they've been

diagnosed with the disease biochemically. It also shows that some surgical criteria have a greater impact on reducing the delay than other criterion.

However, there are several limitations to this study. As stated in the publication, the goal of the study was to evaluate the impact of surgical guidelines on the time course to surgical referral. However, the study opted to use surgery date as a surrogate for time to referral because all surgeries were completed at a single surgery center and the study indicated that patients typically undergo surgery shortly after their initial consultation. However, the study did not expound on how long patients usually wait between surgical consult and completion of surgery, and therefore we don't know how much shorter the time course would have been if referral date had been used as the endpoint. There are several reasons surgery could be delayed after a referral is made including patient and provider scheduling limitations or the need for additional biochemical tests or imaging before surgery. Another limitation to the study is the way it applied surgical criteria to classify patients into study groups. Because the study examined patients who underwent surgery in 2013, they chose to use 2008 surgical guidelines with the addition of 24-hr urine calcium and history of nephrolithiasis from 2013 guidelines. However, they did not include measurement of CrCl or presence of nephrocalcinosis or vertebral fractures in their definition of patients who meet surgical criteria even though these are part of the 2013 guidelines.[15] Our study aims to do a more comprehensive analysis of the impact of 2008 and 2013 surgical criteria on time course to surgical referral. Another concern about this study design is that it defines diagnosis as the date the ICD-9 code for PHPT was entered into the patient's chart. This relies both on recognizing inappropriately elevated PTH in the setting of hypercalcemia as a diagnosis of PHPT and on clinicians entering

the diagnosis in the patient's chart, which could be delayed due to a number of factors. It is well documented that even when PTH is measured, physicians are underrecognizing PHPT.[16] Our study avoids this by relying only on biochemical data for diagnosis.

Mallick et al. is another important study to consider as it is the only study that examines racial disparities in time from diagnosis to parathyroidectomy in Black and non-Hispanic White patients with PHPT. This study analyzed health records for 2,289 patients who had at least one elevated serum calcium level and an inappropriately elevated PTH value (> 21 pg/mL). Time course was from index high calcium (> 10.5 mg/dL) to parathyroidectomy, determined by ICD-9 and ICD-10 codes. Study groups were determined by race and gender. Similarly to Naples et al., the mean follow up time for all patients was 28.3 ± 19.3 months. Black males experienced the longest delays from hypercalcemia to surgery with a median of 13.6 months (IQR 2–28) compared with 2.9 months (IQR 1–8) for non-Hispanic White males ($p < 0.05$). Black women waited a median of 6.7 months (IQR 2–16) versus 3.5 months (IQR 2–14) for non-Hispanic White women ($p < 0.05$). Black patients were also less likely overall to undergo surgery compared to non-Hispanic White patients. One year after initial elevated calcium, 6% of Black males underwent surgery compared to 20% of non-Hispanic White males and 13% Black females underwent surgery compared to 20% of non-Hispanic White females.[17]

This study is important because it reinforces findings from Naples et al. that overall, patients with PHPT are waiting approximately four years between diagnosis and surgery. It also demonstrates that there are indeed greater delays among Black patients with PHPT compared to non-Hispanic White patients. However, the study had several design weaknesses. Firstly, the first elevated serum calcium value was used as the start

point. However, PTH is not a routinely ordered test, so patients are not likely to have PTH measured at the same time hypercalcemia is reported on routine bloodwork. PTH is essential for the diagnosis of PHPT and physicians would not be expected to refer patients for surgery until hypercalcemia and inappropriately elevated PTH is observed. Therefore our study design uses the second elevated serum calcium measurement as the start point. This study also does not indicate how the patient race was determined. We do not know if race was self-reported or if it was obtained from the EHR. It is also unknown whether patients who identify as more than one race or as Hispanic-Latino ethnicity were included This could introduce confounders into the study. A limitation of the study is that it did not racially stratify objective surgical guidelines and assess whether they had an impact on time course from hypercalcemia to surgery. This is a limitation that our study aims to address.

Review of Studies to Identify Possible Confounding Variables

Age

Age has consistently been shown to influence whether a patient with PHPT is referred to or undergoes surgery and therefore is an important confounding factor to examine. A retrospective cohort study aimed at examining surgery underutilization and delay in treatment among the elderly, found that the likelihood of surgery decreased linearly among patients older than 60 years old compared to those 50-59 years old. The odds ratio for ages 60-69 was .68 ($P<0.05$), .41 for ages 70-79 ($P<0.0001$), and .11 for ages $\geq$ to 80 ($P<0.0001$). Using a Cox proportional hazards model and controlling for various confounders, the study also determined that all elderly age groups experienced greater delays from diagnosis to surgery compared to patients less than 60 years old. Mean interval for patients less than 60 years old was 12.4 months, whereas the interval

ranged from 14.8 months to 16.2 months for the elderly age groups.[18] Another retrospective cohort study examining the characteristics of patients who underwent parathyroidectomy found that patients who underwent surgery were younger (mean age 62.4 [SD 11.4]), on average, than patients who were managed non-operatively (mean age 67.1 [SD 12.4]; p<.001). Patients aged 75-84 at diagnosis had 50% lesser odds of undergoing parathyroidectomy (OR 0.50 [95% CI 0.45e0.55]) and patients aged 85 or older had 79% lesser odds of parathyroidectomy (OR 0.21 [95% CI 0.17e0.26].[19] Although these two studies assessed patients who eventually underwent surgery, Balentine et al.'s study assessed the characteristics of patients with PHPT who were referred to surgeons. The study identified 10,432 patients with hypercalcemia between 2011-2015 and found that surgical referrals decreased for older (OR .27 for age > 85 years) and younger age ranges (OR .42 for age < 35 years).[20] These studies imply that hesitancy to refer and surgically treat elderly patients within PHPT exists, possibly due to decreased life expectancy or increased comorbidities, despite studies that have demonstrated parathyroidectomy success rates of 98% and cost-effectiveness in patients with predicted life expectancy of 5 years or more.[18] Our study will collect data on mean age as well as age categories based on the results of the prior studies summarized above.

Gender

Gender is another important confounding variable to consider as gender has been shown to influence likelihood of surgical referral and odds of undergoing parathyroidectomy among those with diagnosed PHPT. A retrospective cohort examined the cumulative incidence of parathyroidectomy and used Cox proportional hazards regression models to assess for the association of several variables. Although external validity of the study is limited by the study's use of Medicare claims to identify patients

and therefore limiting the age of the study population to those greater than 65 years old, the study found that female sex was associated with an increased likelihood of parathyroidectomy (aHR 1.18 ;95% CI 1.11, 1.25).[21] As described previously, Balentine et al.'s study examined the characteristics of patients with hypercalcemia referred to surgeons at the University of Alabama and found that male gender predicts against surgical referral (OR .78).[20]

Education

Education is a variable that, in combination with income and insurance, may serve as a surrogate for SES or as an indication for health literacy. Racial and ethnic disparities continue to endure in education as evidenced by Black people attending high-poverty schools more often and experiencing a higher rate of withdrawing from high school compared to non-Hispanic White people.[22] Kapoor et al.'s study aimed at identifying predictors of appropriate follow-up of incidental findings on lung cancer screening scans found that higher education level was strongly associated with appropriate follow-up (65% versus 40%, P = .02).[23] Studies with other screening modalities have demonstrated similarly that education and healthcare literacy are strong predictors of appropriate clinical follow-up.[24-27] These studies suggest that lower education may impact a patient's understanding of disease processes and influence timely follow-up of abnormal clinical results. Therefore, it is necessary to include education level in our analysis as a possible confounding variable. Education level will be determined from data in the patient's medical chart and described in more detail in Chapter 3 - Study Methods.

SES

Income and insurance coverage are variables often used as a proxy for social economic status.[28] It is well documented that low SES can affect patients' ability to

access timely and quality healthcare. An examination of 58 systematic reviews found that when compared to other high-income countries, financial factors were most often cited in the USA as being a barrier to seeking care.[29] A study on treatment of hernias reinforced this as it found that individuals of lower SES more often presented with a delay due to a myriad of barriers including decreased understanding of the disease, provider mistrust, reduced access to physicians and preventative care, and variations in the specialty referral process.[30] Patel et al.'s study examining the relationship of socioeconomic disparities and cancer severity at presentation found that uninsured patients (OR 1.36, $p < 0.01$) and patients with Medicaid (OR 1.22, $p < 0.01$) were significantly more likely to have a late stage at presentation.[8] Similarly, a study examining disparities in non-small-cell lung cancer found that patients in the highest median income category were 30% more likely to receive timely treatment compared to those in the lowest median income category.[9]

Not only have income and insurance coverage been shown to influence timely disease management, there is also clear evidence that a higher percentage of Black Americans live in poverty and experience higher unemployment rates than non-Hispanic White Americans.[22] In 2003, 1 in 5 Black people were uninsured compared to 1 in 10 non-Hispanic White people.[31] As demonstrated in Kuo et al.'s study examining the relationship between race and thyroid disease severity, 73.1% of Black patients enrolled in the study were in the lowest income quartile compared to 18.8% of non-Hispanic White patients enrolled in the study.[5] Because any of the burdens related to low SES such as access to physicians, cost of laboratory testing and insurance copays, and insurance coverage of specialists and surgical treatment, can influence the timely receipt of a surgical referral for PHPT, it is essential that our study analyze the median income,

insurance coverage, and insurance change since diagnosis for our study population. Our study will aim to determine median income level similarly to Kuo et al. which matched patient's home zip code to median income for that zip code according to the United States Census Bureau.[5] Insurance coverage and insurance coverage change during the study period will be determined using data from the patient's electronic health record which is explained in more detail in Chapter 3 – Study Methods.

Distance from Home to Referring Facility

Increased distance from healthcare facilities and higher burden of travel time may also influence a patient's ability to attend follow-up appointments and desire to seek surgical care especially if longer travel times are associated with increased costs or loss of wages. A cross-sectional analysis examining the geographic and racial differences in travel burden for medical services found that rural residency was associated with increased odds of traveling 30 miles or more (OR, 1.80, CI 1.09 2.99) and that Black race was associated with increased odds of a trip lasting 30 minutes or longer (OR 3.04. 95% CI 2.0 4.62).[32] In Shugarman et al.'s study of disparities in non-small-cell lung cancer, rural residency was associated with a 7.7% lower predicted probability of appropriate and timely chemotherapy treatment compared to urban residents (22.8% vs. 30.5%).[9] Similarly, a study examining factors associated with delay in mammogram follow-up found that women who lived closest to their diagnosing medical facility were more likely to complete their work- up (HR = 1.41; 95% CI = 1.00-1.80).[33] Using the zip code associated with the patient's listed address in their electronic health record at time of diagnosis in combination with the zip code of the referring physician's office, we aim to calculate an approximate distance from home to referring facility to assess for a confounding relationship between referral delay and travel burden.

Comorbidities

The presence of comorbidities is well known to affect many aspects of medical decision-making and treatment across medical specialties. One study found that patients with greater burden and severity of comorbid diseases who were recently started on dialysis were more likely to be evaluated late by a nephrologist compared to patients with fewer and less severe comorbidities.[34] There have been similar findings across studies related to PHPT. Balentine et al.'s study found that patients with PHPT without any Elixhauser comorbidities were more likely to be referred to surgeons (OR of 2.3).[20] Similarly, Seib et al.'s retrospective study found that patients who underwent parathyroidectomy had fewer comorbidities than patients managed non-operatively (mean CCI 0.95 [SD 1.38] vs 1.49 [SD 1.8]; $P < .001$). Patients with increased comorbidity burden according to the Charlson Comorbidity Index had 38% lesser odds of undergoing surgery (OR 0.62 [95% CI 0.58-0.66] for CCI ≥ 2 vs 0).[19]

Not only are comorbidities associated with decreased odds of being referred to or undergoing parathyroidectomy, studies have also demonstrated that Black patients have a higher prevalence of many comorbid conditions compared to non-Hispanic White patients. Hedley et al.'s prevalence survey of overweight and obese adults examined a representative sample of US noninstitutionalized civilians and showed that both Black women and men had a higher prevalence of extreme obesity (BMI > 40) compared to their non-Hispanic White and Mexican American counterparts. Black women had the highest prevalence of extreme obesity at 13.5% compared to 5.5% and 5.7% of non-Hispanic White and Mexican American women.[35] Other studies have shown that despite only constituting 13% of the population, Black people encompass 35% of the people receiving dialysis for kidney failure.[10] There is also a higher prevalence of diagnosed type

2 diabetes mellitus (DM) among Black people (12% vs. 7% non-Hispanic White) and Black people experience a disproportionate number of complications related to DM including hypertension and stroke.[36] A recent cohort study of 5,902 patients being treated for COVID-19 infection, used the Charlson Comorbidity Index to determine that Black patients had a higher proportion of more than 2 medical comorbidities compared with non-Hispanic White patients (39.5% vs. 28.9%, $P < .001$).[37] Because prior studies indicate that comorbidities influence PHPT treatment and there is increased prevalence of many comorbid conditions among Black people, it is essential to include a comorbidity score in our analysis of potential confounding variables.

Calcium Level

Serum calcium level at the time of diagnosis has been shown to influence completion of diagnostic workup, referral to specialists and parathyroidectomy rates. A large prevalence study analyzed 7,269 patient records with hypercalcemia between 2008-2009 and found that more severe hypercalcemia was associated with increased rates of obtaining PTH levels.[16] PTH is essential for diagnosing PHPT which suggests that providers are more adept at recognizing PHPT when patients present with more severe hypercalcemia on bloodwork. Because the degree of hypercalcemia has not been shown to consistently correlate with an increased symptom burden, differences in diagnostic work-up and rate of surgical referral are more likely related to provider knowledge and discretion than symptomatology related to the degree of hypercalcemia.[19,38,39] A retrospective study by Yan et al. stratified 2,266 patients with PHPT by normocalcemia (10.0-10.3 mg/dL), moderate hypercalcemia (10.4-11.2 mg/dL) and severe hypercalcemia (11.3 mg/dL) and found that higher calcium levels were correlated with higher surgical rates (12% vs. 27% vs. 46% respectively, $p<0.01$).[40] Enell et al.'s 2018 study examining

characteristics of patients with a biochemical diagnosis of PHPT and their influence on specialty referral practices found that patients assessed by a specialist in endocrinology or endocrine surgery had statistically significant higher serum calcium than those who were not referred (2.65 vs. 2.54 mmol/L, $p < .000001$).[38]

Consensus surgical guidelines published by the Fourth International Workshop for the Management of Asymptomatic Primary Hyperparathyroidism specifies serum calcium level greater than 1 mg/dL above normal as a definitive indication for surgery.[15] A study by Naples et al. evaluated the time course from hypercalcemia to surgery between patients who met at least one surgical guidelines and patients who did not and found that calcium greater than 1 point above the upper limit of normal was one of the strongest indicators of a faster time course from diagnosis to surgery (1.1 ± 0.6 years vs. 2.3 ± 0.2 years, $P = .06$).[14] Therefore, we will assess our study population's mean index calcium level as well as determine which patients present with serum calcium greater than 1 mg/dL above the upper limit of normal according to our laboratory's assay (11.3 mg/dL).

PTH Level

Similarly to serum calcium level, PTH levels also influence whether patients with PHPT receive a surgical referral. In Balentine et al.'s study, patients with PTH levels above the upper limit of normal were more often referred for surgery than patients who had PTH levels within the normal reference range and yet were inappropriately high for their calcium level. Twenty-nine percent of patients with PTH levels above the upper limit of normal were referred whereas only 21% of patients with PTH between 66-85 were referred and 8% of patients with PTH between 21-65 were referred.[20] In Boone et al.'s study examining factors associated with symptoms and PHPT disease severity,

patients with PTH > 100 pg/mL were more likely to have osteoporosis regardless of calcium level (44% vs 38%, P< .001 for Ca ≤ 11 mg/dL) and Ca >11 mg/dL (43% vs 37%, P < .001). PTH levels above 100 pg/mL were also associated with a diagnosis of CKD stage III or worse (33% vs 26%; P < .001).[41] Although our study excludes patients with stage IV or V CKD, stage III CKD has been associated with decreased rates of parathyroidectomy.[19] Although there are no studies that specifically assess whether stage III CKD decreases the likelihood of receiving a referral for parathyroidectomy, there is evidence that a higher comorbidity index does.[20] Therefore, it is important to evaluate serum PTH has a possible confounding variable. We will assess mean PTH as well as degree of PTH elevation to examine whether time to referral is associated with PTH that is inappropriately high but still within normal range (21-64 pg/mL), outside the upper limit of normal (65-99 pg/mL) or severely abnormal (≥ 100 pg mL) according to the laboratory assay used by Yale New Haven Health System.

Surgical Consensus Criteria

According to Seib et al.'s retrospective cohort study, patients with at least one indication for parathyroidectomy, including age <50 or diagnosis of osteoporosis, nephrolithiasis or stage III CKD, had a moderate but not statistically significant increased likelihood of parathyroidectomy.[19] Although published in 2021, this study did not include all surgical guidelines from the 2013 consensus guidelines in its analysis. Other relevant indications for parathyroidectomy include vertebral fractures, elevated 24-hour urine calcium and presence of nephrocalcinosis.[15] A more rigorous study from the Cleveland Clinic Foundation assessed delays in diagnosis and surgical management among patients who met an indication for surgery versus those who did not. Objective criteria included age < 50 years, calcium > 11.5 mg/dL, eGFR < 60 mL/min, 24-hr urine calcium > 400

mg/dL, diagnosis of osteoporosis, or history of nephrolithiasis. The study found that patients who met one objective surgical criterion experienced a mean time from initial hypercalcemia to surgery of 3.9 ± 0.3 years (P=.87). Patients who did not meet one objective experienced a similar delay at 3.8 ± 0.5 years. However, patients who met > 1 objective criterion had a shorter delay (2.7 ± 0.4 vs 4.8 ± 0.4 years, P < .001) than those who met only one objective criterion. Although data from these previous studies are mixed, neither study assessed time course from hypercalcemia to referral and neither stratified by race. Therefore, this is an important potential confounder to include in our study despite an unclear association in previous studies.

Review of Studies to Identify Variables for Secondary Analysis

The Fourth International Workshop on the Management of Asymptomatic PHPT published updated guidelines in 2013 to identify patients with PHPT who would benefit from surgery based on objective criteria.[15] Several studies have shown that some of these objective criteria confer a greater probability of referral to or completion of parathyroidectomy. However, none of these studies stratify objective criteria by race. There are also many studies that suggest Black patients may be protected from some of these disease complications.[3,42-47] Therefore, our study will include a secondary analysis that examines these objective criteria and analyze differences between race and the impact of these variables on time course to parathyroidectomy referral.

Renal Complications

The renal complications associated with PHPT and included in the consensus surgical guidelines include hypercalciuria > 400 mg/dL, moderate to severe CKD (eGFR or CrCl < 60 mL/min), nephrocalcinosis and nephrolithiasis.[15]

Multiple studies have demonstrated lower levels of calciuria among Black people with and without PHPT compared to non-Hispanic White people. One study examined data from seven clinical trials and found that urine calcium was consistently lower in Black women (11-197 mg/24-hr) compared to non-Hispanic White women (21-221 mg/24-hr) even after adjusting for vitamin D levels ($P < 0.0001$) and calcium intake ($p < .001$).[42] Another study analyzed the urine composition of Black and non-Hispanic White post-menopausal women and found that Black women excreted 65 mg/24-hr less urinary calcium ($P < .001$) compared to non-Hispanic White women.[43] These findings persist among Black patients diagnosed with PHPT.[3,44] Fieber et al.'s retrospective study examining racial disparities in PHPT found that Black patients had lower preoperative 24-h urinary calcium levels compared to non-Hispanic White patients (260 vs. 293 mg/24-hr, $p = 0.022$).[3] Another retrospective study evaluating the prevalence of low urine calcium in Black patients with PHPT found that median urine calcium/creatinine was 122 mg/g versus 214 mg/g for Black and non-Black patients respectively ($P=.006$).[44]

Only one study included 24-h urine calcium in its analysis of factors that influence time course to PHPT diagnosis and treatment, and it found 24-hr urine calcium levels did not have an impact.[14] However, elevated urine calcium is commonly considered a risk factor for kidney stone formation.[4,48] Only two prior studies analyzed the association between race and a history of nephrolithiasis in patients with PHPT. Barker et al. did not find a difference in proportion of Black and non-Hispanic White patients with nephrolithiasis. However, the study reported that 10 Black patients had "objective symptoms" of nephrolithiasis, mental status change, or pancreatitis, so it is not clear how many of the 10 patients had nephrolithiasis. The study was also limited by

sample size. Only 36 Black patients and 36 non-Hispanic White patients were enrolled making it difficult to determine significance of any one objective measure.[49] Feiber et al.'s more robust study found that nephrolithiasis was significantly less common among Black patients compared to non-Hispanic White patients (14.0% (41/292) vs. 21.2% (440/2072), $p = 0.004$) which substantiates prior studies that the risk of stone formation in Black patients is decreased at least in part because of lower urine calcium excretion.[3]

Evidence regarding the association between nephrolithiasis and time to referral or probability of undergoing parathyroidectomy are mixed. Seib et al.'s analysis of factors contributing to likelihood of undergoing parathyroidectomy found that patients with nephrolithiasis were significantly more likely to undergo surgery compared to those that did not (49.6% vs 36.3%; $P < .001$).[19] However, Naples et al. did not find that patients with nephrolithiasis had a faster time course to diagnosis and surgery compared to those without nephrolithiasis ($P=.41$). One limitation, however, is that only 48 patients had nephrolithiasis and therefore were included in the analysis. In contrast, Seib et al.'s study included 3,630 patients with nephrolithiasis so their results may be more robust.

Nephrocalcinosis, the deposition of calcium in the parenchyma and tubules of the kidneys, is associated with urinary calcium excretion and stone formation. Increased excretion of calcium through the tubules can lead to deposition in the kidneys which can then lead to stone formation. Nephrocalcinosis is not often included in studies that examine factors contributing to diagnosis and referral delays in PHPT, so not much is known about whether there are racial differences in this disease manifestation or if its presence may affect a patient's time course to referral. However, it is logical to assume

that since there is evidence of decreased urine calcium excretion and nephrolithiasis among Black patients with PHPT, nephrocalcinosis may also be less common.

Besides being included in consensus guidelines for surgical referral, assessing the presence of hypercalciuria, nephrolithiasis, and nephrocalcinosis is essential for two reasons: prior studies suggest racial differences may exist regarding the likelihood of Black and non-Hispanic White patients with PHPT presenting with these complications, and these disease sequelae may significantly affect the time from disease presentation to referral for surgery. Disparities in time to referral based on individual surgical criterion may be related to a physician's awareness of the indications for parathyroid surgery, their ability to recognize these signs and symptoms as related to parathyroid disease, or the ability to understand the impact these symptoms may have on a patient's quality of life and desire for definitive treatment.

Evidence of chronic kidney disease (CKD) is also a surgical criterion for PHPT. Most recent guidelines suggest using CrCl < 60 mL/min as indicating a need for surgery while 2008 guidelines assess kidney function with eGFR < 60 mL/min.[15,50] Our study will collect data for both CrCl and eGFR since physicians may be using either of these measurements to identify candidates for surgical referral. CrCl assessment is challenging as it requires urine collection which is often performed incorrectly by patients. Physicians may instead be inclined to assess eGFR which is a calculation based on serum creatinine, age, gender and race. However, there is concern that the race-based adjustment for Black patients in eGFR calculations may incorrectly overestimate kidney function.[51] This is significant in PHPT because studies have identified racial disparities in eGFR and kidney function and increased comorbidity burden have been shown to influence probability of

undergoing parathyroidectomy.[19,20] Fieber et al.'s retrospective analysis of racial disparities in PHPT found that Black patients had higher preoperative eGFR compared to non-Hispanic White patients (84 vs. 76 ml/min/ 1.73 m2, $p < 0.001$)[3] while Seib et al. found a diagnosis of stage III CKD (eGFR 30-59) predicted against undergoing parathyroidectomy (OR 0.79 [95% CI 0.71e0.89]).[19] When considering delays in diagnosis and completion of surgery however, Naples et al.'s did not find that eGFR significantly affected the time to diagnosis or surgery for patients with PHPT.[3] Our study will compare mean eGFR and CrCl between study groups as well as determine how many patients meet the surgical consensus guidelines of eGFR or CrCl < 60 mL/min to determine racial differences in kidney function in these patients and whether it influences time from diagnosis to surgical referral.

Skeletal Complications

Patients with PHPT are at risk for developing skeletal complications such as osteoporosis and fragility fractures. Chronically elevated PTH leads to the release of calcium from bones which eventually causes them to become brittle, weak and be at greater risk for fracture.[52,53] The 2013 consensus guidelines identify osteoporosis (BMD < -2.5) at the lumbar spine, total hip, femoral neck or distal 1/3 radius, or vertebral fracture by x-ray, CT, MRI or VFA as criteria to recommend patients for surgery.[54] The 2008 guidelines are slightly more broad and identify osteoporosis at any site and any previous fragility fracture as indications for surgery.[50] Because our enrollment period begins in 2014 and some physicians may opt to make referrals based on the more conservative guidelines published in 2008, our study will collect data on skeletal complications from both sets of published guidelines. We will identify patients with osteoporosis at any site, patients with a history of prior fragility fracture and patients with

vertebral fracture on imaging. Many studies on PHPT also include osteopenia (BMD between -1 and -2.5) in their analysis as it is evidence of skeletal complications that have not yet progressed to osteoporosis and may influence a provider or patient's desire for surgical referral to prevent further skeletal breakdown.[55]

There are clear racial differences in the prevalence of osteoporosis. A study by the National Health and Nutrition Examination Survey from 1999-2014 found that the prevalence of osteoporosis was significantly lower in Black patients (1.7%) compared with non-Hispanic White people (3.7%), Hispanic (4.1%) and other races (5.9%).[45] Black people also have a lower risk of fragility fractures, a complication of osteoporosis, compared to other populations.[46,47] One theory about why Black people have some protection against osteoporosis and fractures is that they experience skeletal resistance to parathyroid hormone and their kidneys are better able to reabsorb calcium. This is reinforced by studies that have shown decreased urine calcium in Black populations.[56,57] There are not many studies that examine racial differences in prevalence of osteoporosis and fractures in patients with PHPT. However, Fieber et al.'s 2021 study examining racial disparities in PHPT found that bone mineral density loss was significantly less common in Black patients compared to non-Hispanic White patients (59.9% (109/182) vs. 74.6% (1163/1559), $p < 0.001$).[3] Studies that have examined the relationship between skeletal complications and referral to or completion of parathyroidectomy have shown mixed results. In Seib et al.'s retrospective analysis, parathyroidectomy rates were similar among patients with and without a diagnosis of osteoporosis (22.2% vs 39.5%) although having osteoporosis still significantly increased the odds of undergoing surgery 1.15 [95% CI 1.08-1.22].[19] Naples et al. found no impact of osteoporosis on time course to

diagnosis or surgery in patients with PHPT. However, all patients with osteoporosis underwent surgery sooner overall than patients without osteoporosis.[14] Another retrospective cohort study examined the prevalence of undiagnosed and unrecognized PHPT and found that patients with osteoporosis were not more likely to receive a surgical referral than those without. However, the study included three study groups: patients who had PHPT documented as a diagnosis in their chart, patients who had PTH obtained but did not have a diagnosis of PHPT in their chart, and patients who did not have PTH obtained. Only 52% of the patients with osteoporosis had PTH documented in the EHR which is an essential element to making the diagnosis of PHPT. Therefore, it can be assumed that many of the patients in the study with osteoporosis were never diagnosed with PHPT by a physician who could have made a referral to endocrine surgery.[16] A prospective cohort study of 74 patients who underwent parathyroidectomy included an assessment of why their physician referred them for surgery and the most common reason for referral was decreased bone mineral density on DXA scan (74% of patients).[58] Although results from previous studies are mixed, there are no studies that examine racial differences in disease complications and how they may influence time course from diagnosis to surgical referral. Since osteoporosis and fragility fractures are identified as objective surgical criteria and Black patients may have some amount of protection against these complications, it is important to include these in our secondary analysis.

Vitamin D (25(OH)D)

We will include measurement of 25-hydroxyvitamin D [25(OH)D] in our secondary analysis because it is identified as part of the work-up for PHPT according to the American Association of Endocrine Surgeons, and it has an important association with PTH and bone mineral density. Vitamin D deficiency is defined as the threshold

below which patients begin to experience increased bone turnover and mineral loss. This has been identified as between 30 and 90 nmol/l in different populations.[59] Vitamin D deficiency and insufficiency are common within the PHPT population and some studies postulate that it may exacerbate PTH secretion, accelerate adenoma growth and hasten skeletal deterioration.[60-62]

It is also important to include 25(OH)D in our analysis because there are clear racial differences in 25(OH)D levels. Studies have consistently confirmed that Black people have lower 25(OH)D concentrations compared to non-Hispanic White people across all age groups.[63-65] Other studies have examined the relationship of 25(OH)D to PTH and bone mineral density in racially diverse populations. These studies have found that Black patients have significantly lower 25(OH)D and higher PTH concentrations than non-Hispanic White patients. Black patients also don't experience BMD loss with declining 25(OH)D levels like non-Hispanic White and Mexican American patients do and PTH is maximally suppressed at a lower 25(OH)D concentrations in Black patients compared to non-Hispanic White patients.[56,66] Because of these racial differences and association of 25(OH)D with other variables in our study, it is important to assess the mean vitamin D concentration of our study groups.

Completed Work-Up

One study examined racial disparities in preoperative workup for PHPT. Complete preoperative evaluation was defined as measurement of serum calcium, 24-h urine calcium, serum PTH, creatinine, eGFR, and DXA scan for osteoporosis. The study found that Black patients were significantly more likely to have incomplete preoperative evaluation due primarily to significantly lower likelihood of receiving a DXA scan to evaluate for osteoporosis. One limitation to this study is that it did not include evaluation

of fractures or nephrolithiasis and/or nephrocalcinosis in its definition of complete work-up despite those complications being included in the consensus guidelines for surgical management of parathyroid disease.[3] Incomplete PHPT evaluation could lead to a delay in referral to surgery particularly because complications of the disease and fulfillment of surgical criteria cannot be determined accurately without complete evaluation. Although there is only one prior study examining racial differences in completion of preoperative evaluation, healthcare inequalities discussed in previous sections are more common in the Black population and may contribute to disparities in being able to complete the work-up. Therefore, our study will assess whether patients received a complete work-up. Complete work-up will include serum calcium, serum PTH, 24-hr urine calcium, eGFR and/or CrCl, 25-hydroxyvitamin D, DXA scan for evaluation of osteoporosis and vertebral fractures, and abdominal x-ray, ultrasound, or CT imaging for nephrocalcinosis and nephrolithiasis.[67] Fragility fractures will not be included despite being a 2008 surgical criterion because work-up for past fragility fractures is likely accomplished via history taking, and it cannot be easily ascertained by a retrospective review whether physicians completed this portion of the work-up particularly because the absence of pathology is less likely to be documented in the note.

Referral by Endocrinologist

PHPT is often diagnosed and managed by primary care physicians (PCP), but patients can also be referred to and managed by specialist physicians, namely endocrinologists. Many studies have reported evidence of racial disparities in access to specialty services. Bach et al. found that in the US, approximately 20% of physicians provide care for 80% of the Black population and these physicians report disproportionally less access to resources including specialty services.[68] Landon et al.'s

cross-sectional observational study assessing racial disparities in PCP specialty referrals found that Black patients are less likely to receive specialty referrals from PCPs across 6 medical specialties and 12 healthcare markets.[69] Black patients also have lower visit rates in the majority of outpatient specialty offices compared to non-Hispanic White patients (23 of 29 [79.3%]; 17 of 29 [58.6%]; $P < .05$) according to Cai et al.'s examination of nationwide racial disparities in outpatient specialty services.[70]

Some studies have found that patients with PHPT who were seen by an endocrinologist were more likely to undergo parathyroidectomy (OR 1.13 [95% CI 1.07e1.19]).[19] Similarly, Kuo et al. found that patients who satisfied at least one consensus criterion were more frequently referred for surgical consultation when evaluated by an endocrinologist versus a non-endocrinologist (54.2% vs 23.3%, P < 0.01). Endocrinologist evaluation was also associated with increased likelihood of undergoing surgery once referred (OR 1.6, 95%CI 1.1–2.4).[71] Endocrinologists may be more aware of the consensus surgical criteria and also be more adept at recognizing and assessing for disease complications which could lead to a faster time course from diagnosis to surgical referral. Therefore, this is an essential variable to consider for our secondary analysis.

Review of Relevant Methodology

Study Design

In order to examine the effect of race on time to parathyroidectomy referral for patients with PHPT, an observational study design is required. Due to cost and time considerations, the most feasible study design is a retrospective cohort study. A prospective control study would not be possible as it would require following patients for approximately four years according to prior studies.[14,17] It also would prevent analysis of

many variables since manifestations of the disease often occur before diagnosis. There are two existing studies that examine diagnosis and treatment delays in PHPT, both of which utilize retrospective cohort designs. [14,17]

Study Setting

Because our study design aims to collect information on many different study variables, it makes most sense to derive our study population from a large hospital system with a diverse patient population that utilizes a comprehensive EHR system. Yale New Haven Health System has a large network of hospitals and outpatient clinics that use Epic for data collection and storage and has a team dedicated to extracting patient data for research purposes.[72,73] Patients who utilize the Yale New Haven Health System's network are more likely than patients who seek care in small hospital networks or private offices to have much of their health information stored discretely in one searchable medical record. This will enable us to collect all relevant patient data for our proposed analyses.

Exposure

The main exposure variable is race. Although race can be identified through the EHR, there are limitations and concerns about this method. Race in the EHR is not always self-reported. Patients are also not able to identify as more than one race. Multiple studies have found misclassification of race in the EHR most often occurs with individuals who identify as Hispanic which is important to consider since our study excludes patients who identify as Hispanic ethnicity.[74,75] To avoid these potential inaccuracies, prior studies have matched patients to their self-reported US Census data.[3,76] Since accurate race and ethnicity classifications is essential to our study design, we will cross reference each patient's name and date of birth with US Census data to

accurately identify their race. Study groups will be referred to as “Black” and “non-Hispanic White” to be in-line with updated guidelines on reporting race in research.[1]

Outcome

The primary outcome of the study is time from hypercalcemia to referral for parathyroidectomy. Although prior studies aimed at examining treatment delays in PHPT have used parathyroidectomy date as the endpoint, we propose that referral date is a more useful endpoint and eliminates potential confounding variables such as patient and provider scheduling limitations. Naples et al. postulated in their study that time from hypercalcemia to surgery date is an appropriate surrogate for surgical referral because patients in their clinic undergo surgery shortly after consultation. However, they did not specify how long a time period this typically is for their patients and surgical consultation is not synonymous with surgical referral as it can often take weeks to months for patients to see specialist providers following referral. It is unnecessary to use parathyroidectomy as a proxy for surgical referral since surgical referrals are entered in the electronic health record and are associated with an exact date.

The outcome will be operationalized as a time-to-event and reported as median and IQI in months, similar to Naples et al. and Mallick et al. This is the most accurate method for comparing time from diagnosis to referral between study groups since our design makes it possible to obtain exact dates for the elevated serum calcium tests and for the surgical referral. This will also allow us to determine and compare the percentage of each study group who received a referral for surgery in the timeframe of the study.

Recruitment years for this study were determined based on the publication of the most recent surgical guidelines for PHPT in 2013. Recruitment will begin in January 2014 and end in December 2015. Because some clinicians may not be aware of new

guidelines or may still refer patients based on guidelines from 2008, our secondary analysis includes consideration of 2008 and 2013 surgical guidelines. We are unable to recruit patients for more than two years because the follow-up period must end before the COVID-19 pandemic in 2020 when elective surgeries were often cancelled or postponed. However, we expect to have more than an adequate number of participants to sufficiently power our study with a two year recruitment period.

The follow-up period will be four years because two prior studies have demonstrated an approximate delay from diagnosis to parathyroidectomy of four years. Both of these studies specify a start date as first elevated serum calcium and an end date as completion of surgery.[14,17] We anticipate that our time course will be shorter than these prior studies because we will use the second elevated serum calcium as our start date and referral date as our end point. However, there are no studies that estimate the average time patients wait from receipt of a surgical referral to completion of surgery, so without this reference point, we have chosen to preserve a length follow-up period in our study with the goal of capturing as much important and relevant follow-up data as possible.

Selection Criteria

Inclusion criteria will be all Yale-New Haven Health System patients, aged 18 or older, who have two outpatient serum calcium measurements >10.3 mg/dL and PTH > 21 pg/mL between January 1, 2014 and December 31, 2015, and whose race is identified as Black or non-Hispanic White according to the US Census.[16,17] A value of 10.3 mg/dL for serum calcium is based on the upper limit of normal for Yale New Haven Health System's laboratory assay. PTH is a requirement for the study because it helps eliminate patients who have elevated calcium due to conditions other than PHPT. A value of > 21 pg/mL for inappropriately elevated PTH in the setting of hypercalcemia will be used as

this is consistent with prior studies.[16,17,77] Outpatient serum calcium measurements will be used because inpatient serum calcium values are more variable and often related to disease processes other than PHPT. Outpatient laboratory values also helps ensure that patients have a PCP in Yale New Haven Health System's hospital network.

Exclusion criteria will include any patient who identifies as Asian, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, or two or more races according to the US Census. Patients will be excluded if they have multiple endocrine neoplasia 1 (MEN1), familial hypocalciuric hypercalcemia (FHH), or invasive cancer. MEN1 and FHH are both genetic disorders that can cause hypercalcemia in the setting of inappropriately elevated PTH, but they have different disease pathology and present with different symptoms and severity compared to PHPT.[14,38,44] Patients with invasive cancer will also be excluded because parathyroid hormone-related protein (PTHrP) can cause hypercalcemia in these patients.[77] Patients will also be excluded if they have evidence of severe or end-stage CKD (Cr > 2.5 mg/dL or eGFR < 30 mL/min) or a history of renal transplant because these patients may have secondary hyperparathyroidism.[38,77] Patients who have had previous parathyroid surgery will also be excluded because this may indicate an unsuccessful first surgery which would alter the time from hypercalcemia to surgical referral or it may indicate progression of disease due to an underlying genetic condition. Exclusion criteria will also include evidence of thiazide diuretic use or lithium use before or within 3 months after initial elevated serum calcium date because these are drugs known to cause imbalance of calcium and PTH.[38,77,78]

Statistical Analysis

Power calculations were completed based on Mallick et al.'s study because it is the only study that examines racial disparities in time from hypercalcemia to PHPT

treatment. It also enrolled patients based on similar inclusion criteria and therefore we were able to estimate a sample size based on their study population. By comparing the number of patients enrolled in the study and the number of outpatient visits for the health system where the study took place, we were able to estimate the number of patients we would enroll in two years at Yale New Haven Health System with a similar study design. Based on the gender differences in PHPT incidence published in 2017, we estimated the gender composition of our study. We then estimated the percentage of Black and non-Hispanic White patients based on New Haven census data. We then found the minimum effect size needed to power our study at 80% power. This is explained in more detail in Power Calculation section of Chapter 3 – Study Methods.

Statistical analysis for confounding variables and secondary analysis variables is described in more detail in Chapter 3 – Study Methods.

Conclusion

The literature supports a need for this study. There is clear evidence that racial disparities are prevalent across medical specialties and that Black patients present with more severe disease in benign and malignant conditions.[5-7,14] It's also clear that one explanation for this could be diagnosis, referral or treatment delays. One study has already demonstrated that Black patients experience much longer delays from hypercalcemia to parathyroidectomy compared to non-Hispanic White patients.[17] However, the study design has flaws and limitations that our study addresses. It is evident that more studies need to examine the possible reasons for racial disparities in PHPT so that we can implement interventions to decrease these disparities.

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Chapter 3 - Study Methods

Study Design

The proposed study design is a retrospective cohort study within Yale New Haven Health System that will investigate the association between race and time from first known hypercalcemia to parathyroidectomy referral among Black and non-Hispanic White patients at risk for surgical referral between 2014-2015 and followed-up until date of surgical referral or the end of the study period in 2019. Due to the nature of the study, there will be no blinding and the participants will not be notified of their inclusion. Data will be sourced from Yale New Haven Health's electronic health record (EHR) system and the US Census. No identifiable information will be shared other than to match patient records to US Census race data.

Study Population and Sampling

The study population will be individuals ≥18 years old at risk for referral for parathyroidectomy. This is defined by having two outpatient elevated serum calcium measurements > 10.3 mg/dL and inappropriately elevated PTH (> 21 pg/mL) between Jan 1, 2014 – Dec 31, 2015. The study will utilize The Joint Data Analytics Team (JDAT) at Yale New Haven Health System to extract patient charts that fit these criteria in the electronic health record (EHR) system. Patients will then be matched to US Census data and only included if they identify as Black or non-Hispanic White. The study period will end December 31, 2019 allowing for a minimum of 4 year follow up for all subjects. Subjects who fit the inclusion criteria between January 1, 2014 and December 31, 2015 will be assigned into groups based on their race and be followed until they receive a referral for parathyroidectomy or until the study period ends on December 31, 2019. Recruitment into this study will not require any notification to the participants because it

is retrospective and does not require an intervention. Sampling will be a non-random consecutive enrollment of patients between 2014-2015 who meet the previously mentioned criteria.

Inclusion criteria will be all Yale New Haven New Haven Health patients, aged 18 or older, who have two outpatient serum calcium measurements > 10.3 mg/dL and concurrent PTH > 21 pg/mL between January 1, 2014 and December 31, 2015, and whose race is identified as Black or non-Hispanic White according to the US Census.[1]

Exclusion criteria include any patient who identifies as Asian, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, or two or more races according to the US Census. Patients will be excluded if they have diagnoses of multiple endocrine neoplasia 1 (MEN1), familial hypocalciuric hypercalcemia (FHH), or invasive cancer. Patients will also be excluded if they have evidence of chronic kidney disease (Cr > 2.5 mg/dL or eGFR < 30 mL/min), history of renal transplant, previous parathyroid surgery, or evidence of thiazide diuretic use or lithium use before or within 3 months after second elevated serum calcium date. Exclusion criteria will be identified utilizing chart review of patient records. ICD codes to identify invasive cancer were determined from a previous study which used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 140-209 and 235-239.[2] These will be converted to ICD-10 codes as well to identify patients with invasive cancer. FHH diagnoses will be identified by ICD-10 code E83.52 and ICD-9 code 275.42. MEN1 diagnoses will be determined with ICD-10 codes E31.21, E21.0, Z83.41, Z86.39, Z15.81, Z15.89 and ICD-9 codes 258.01, 252.01, V18.11, V12.29, 252.01, V84.81, V84.89. Chronic kidney disease will be identified with ICD-10 code N18.9, N18.4, N18.5 or by

the patient's laboratory data (eGFR < 30 mL/min or CrCl < 30 mL/min) documented at any point before the date of second elevated serum calcium level. Prior renal transplant and prior parathyroid surgery will be identified in the patient's surgical history or from previous surgical encounters in the chart. When identifying these procedures through the surgical history, codes SHX1382, SHX239, or SHX 239 will be used to identify prior renal transplant and SHX19 and SUR1002 codes will be used to identify prior parathyroidectomy. Current or previous thiazide or lithium use will be identified by that patient's current and past medication list in the chart.

Subject Protection and Confidentiality

The Yale University Human Investigation Committee and the Yale Human Research Program will approve all aspects of this study to ensure patient protection and confidentiality protocols are maintained. Completion and maintenance of current HIPPA training will be required for all personnel involved in the study. All patient data will be stored on an encrypted platform and access will require two-factor authentication. Patients will be de-identified and all patients will be assigned a number for identification.

In addition, Yale requires that all data requests be submitted to the JDAT team through an electronic form which identifies the requester and that requires electronic commitment to the Health Insurance Portability & Accountability Act (HIPPA) & Institutional Policy Compliance.

Recruitment

Yale stores patient data in a customized data warehouse system called Helix which is accessible by The Join Data Analytics team (JDAT) at Yale. Participants will be recruited by submitting a data request to JDAT at Yale for patients that meet the study's inclusion criteria within the specified time frame.

Study Variables and Measures

In this retrospective cohort study, the main exposure will be race, Black or non-Hispanic White. This information will be collected from US Census data after patient records are extracted for initial study sampling.

The primary outcome will be time from hypercalcemia to surgical referral for parathyroidectomy reported in months (table 2). This will be recorded as a median and IQI time-to-event variable. The date of collection associated with the second elevated outpatient serum calcium level will be used as the start point. All patients who have an ambulatory referral for endocrine oncology – endocrine surgery will be identified and the date the endocrine surgery referral was entered into the system will be the endpoint. These referrals contain free text fields for Clinical Reason for Referral and for Comments. Referring physicians also have an opportunity to associate ICD diagnosis codes with the referral. To ensure only surgical referrals for parathyroidectomy are collected and not referrals for other endocrine surgical procedures, the referrals will be reviewed for free text or associated diagnoses that reference primary hyperparathyroidism, hypercalcemia, or parathyroid hormone abnormalities. ICD-9 codes we will use are 252.01, V12.29, 252.01 275.42, 252.9, V18.19, V12.29, 227.1, 252.00, 252.01, 239.7, 793.99, 227.1, 259.9, 790.99, 252.01. ICD-10 codes we will use are E21.0, Z86.39, E83.52, E21.5, Z83.49, D35.1, E21.3. D49.7, R93.8, E34.9, R79.89.

Table 2 - Median time to parathyroidectomy referral by race

Demographic	Total who received referral	Median time (mo)
Non-Hispanic White	%	Median, IQI
Black	%	Median, IQI

Secondary objective variables we will gather to assess presence of surgical indications and complete work-up (table 3) include 24-hour urine calcium, eGFR, CrCl

and vitamin D. These will be treated as continuous parametric variables. 24-hour urine calcium > 400 mg/dL, eGFR < 60 mL/min and CrCl < 60 mL/min will be treated as dichotomous variables. The highest value of 24-hour urine calcium between two years prior to second elevated serum calcium and date of the surgical referral or study end date will be collected from each patient's laboratory data in the EHR. For eGFR, CrCl and vitamin D, the lowest value within that timeframe will be used. Osteopenia, defined as T-score < -1 and > -2.5, and osteoporosis, defined as T-score < -2.5, will be identified by DXA scan reports in the patients' charts. If more than one DXA scan exists, the lowest T-score between two years prior to date of second elevated serum calcium until surgical referral or study end date will be used. PCP office visit notes, endocrinology office visit notes, ultrasound reports, CT results, MRI results, plain film x-ray reports and ICD diagnosis codes will be reviewed to identify patients with nephrocalcinosis, nephrolithiasis, vertebral fractures, and fragility fractures. These will be treated as dichotomous variables. Nephrocalcinosis codes include ICD-10 E83.59, N29 and ICD-9 275.49. Nephrolithiasis will be identified by ICD-10 N20.0 and ICD-9 592.0. Vertebral fractures will be identified by ICD-10 M80.88XA and ICD-9 733.13, 733.00. Fragility fractures will be defined as fractures of the hip, thoracic or lumbar spine, and distal forearm and identified by ICD-9 codes 820, 73314, 8052, 8054, 8234, 81341-81345, 81350-81354, 73312. Completed work-up will be treated as a dichotomous variable and will be defined as a patient who has serum 25-hydroxyvitamin D measured, CrCl measured or eGFR calculated, 24-hour urine calcium obtained, DXA scan completed, and ultrasound, CT or MRI completed for nephrocalcinosis/nephrolithiasis. [3] Each chart will be examined for study variables two years prior to first documented elevated serum

calcium to date of surgical referral or study end date. We will also determine the percentage of patients in each study group who received their surgical referral from an endocrinologist by determining the medical specialty of the provider associated with the referral.

Table 3 - Surgical criteria presentation by race

	Black	Non-Hispanic White	P value
24 hr Urine calcium (mean +/- SD)	Mean +/- SD	Mean +/- SD	t-test
24 hr Urine calcium (mg/dL) >400 mg	%	%	Chi-square
eGFR (mean +/- SD)	Mean +/- SD	Mean +/- SD	t-test
eGFR <60 (mL/min)	%	%	Chi-square
CrCl (mean +/- SD)	Mean +/- SD	Mean +/- SD	t-test
CrCl < 60 mL/min	%	%	Chi-square
Nephrocalcinosis	%	%	Chi-square
Nephrocalcinosis	%	%	Chi-square
Osteopenia	%	%	Chi-square
Osteoporosis	%	%	Chi-square
Vertebral fracture	%	%	Chi-square
Fragility fracture	%	%	Chi-square
Vitamin D (mean +/- SD) (ng/dl)	Mean +/- SD	Mean +/- SD	t-test
Completed work-up	%	%	Chi-square
Referral by endocrinolist	%	%	Chi-square

Confounding

The confounding variables accounted for in this study are summarized in table 1. The two groups, Black patients and non-Hispanic White patients, will be characterized by the following demographics: mean age, age group (18-35, 36-50, 51-64, 65-74, 75-84, >85), gender, highest completed education, median income and median income group ($1-35,999, $36,000-44,999, $45,000-58,999, >$59,000).

Age, gender and highest completed education will be collected from the patient's chart. Age will be specified at the date of second elevated serum calcium level. Education will be extracted from the history portion of the patient's chart and the most recent documentation within the study period will be used. Documentation of 1st-12th grade, high school graduate, GED, or never attended will be categorized as "high school or less". Documentation of some college or associate degree will be categorized as "some college." Documentation of bachelors, doctorate, masters, or professional will be

categorized as “college/graduate/professional.” Documentation of “not asked” and “pt refused” will not be recorded. If a patient has an encounter with documentation of “not asked” or “pt refused” but has a previous encounter within the specified timeframe of one of the other responses, we will use that documentation to classify the patient’s education. Median income and median income group will be identified by matching the patient’s zip code to median income from the US census for that particular zip code. Historical zip codes will be obtained to account for patient’s moving and the patient’s zip code at the time of second elevated serum calcium test will be used. Historical zip codes are stored in EPT 2410 within table PAT_ADDR_CHNG_HX and will be obtained through JDAT.

Other confounding variables this study will account for include insurance type, insurance change during the study period, distance from home to referring facility, Charlson comorbidity index (CCI), index calcium level, index calcium level ≥11.3 mg/dL, index PTH level, index PTH level group and whether a patient meets at least one consensus criteria for surgery. Insurance type will be categorized by Medicare, Medicaid, private, or uninsured/self-pay. This study will categorize insurance type by determining patients’ primary insurance at the time of second elevated serum calcium test. The financial class of the insurance listed in the patients’ charts will be used to determine the appropriate category. Insurances with financial class Medicare or Medicare Managed Care will be categorized as “Medicare”. Insurances with financial class Medicaid or Medicaid Managed Care will be categorized as “Medicaid”. All other financial class types including BCBS, Commercial and Managed Care will be classified as “Private”. Patients who do not have a primary insurance documented in their chart or who are documented as “self-pay” will be classified as “Uninsured/Self-pay”. Secondary health

insurance will not be accounted for in this study. Patients who undergo a primary insurance change between the period of second elevated serum calcium test and surgical referral date or study end date will be included in the continuous variable "insurance change during study period." Distance from home to referring facility will be determined with the patient's zip code at time of second elevated serum calcium level and the zip code of the referring facility to determine a median distance in miles. Again, historical zip codes will be obtained through JDAT. Comorbidities will be taken into account using the Charlson Comorbidity Index which is a method of categorizing comorbidities using ICD codes from the patient's electronic medical record. Each patients' highest calcium level between the two initial values used to determine inclusion in the study will be used to determine mean index calcium level and index calcium level ≥11.3 mg/dL. Each patient's highest PTH level following the first elevated serum calcium level will be used to determine mean PTH and PTH group. A patient will be included in "meet at least one consensus criteria for surgery" if they meet one of the following criteria: 50 years of age or younger, serum calcium ≥ 11.3 mg/dL, 24-hr urine calcium > 400 mg/dL, eGFR or CrCl < 60 ml/min, evidence of osteoporosis, nephrocalcinosis, nephrolithiasis, vertebral fracture or fragility fracture.

Table 1 - Descriptive Statistics			
	Black	**Non-Hispanic White**	**P value**
Demographics			
Age, y	Mean, SD	Mean, SD	t-test
Age Group			
18-35	(%)	(%)	Chi-square
36-50	(%)	(%)	Chi-square
51-64	(%)	(%)	Chi-square
65-74	(%)	(%)	Chi-square
75-84	(%)	(%)	Chi-square
≥85	(%)	(%)	Chi-square
Gender			
Female	(%)	(%)	Chi-square
Male	(%)	(%)	Chi-square
Highest Completed education			
Highschool or Less	(%)	(%)	Chi-square
Some college	(%)	(%)	Chi-square
College/graduate/professio	(%)	(%)	Chi-square
Insurance Type			
Medicare	(%)	(%)	Chi-square
Medicaid	(%)	(%)	Chi-square
Private	(%)	(%)	Chi-square
Uninsured/Self-pay	(%)	(%)	Chi-square
Insurance change during study period	(%)	(%)	Chi-square
Median Income	Median, IQI	Median, IQI	Wilcoxon rank-sum
Income			
$1-35,999	(%)	(%)	Chi-square
$36,000-44,999	(%)	(%)	Chi-square
$45,000-58,999	(%)	(%)	Chi-square
≥$59,000	(%)	(%)	Chi-square
Distance from Home to Referring Facility (miles)	Median, IQI	Median, IQI	Wilcoxon rank-sum
Charlson Comorbidity Index			
0	(%)	(%)	Chi-square
1	(%)	(%)	Chi-square
2+	(%)	(%)	Chi-square
Index calcium level (mg/dL)	Mean, SD	Mean, SD	t-test
Index calcium level group (mg/dL)			
≥11.3	(%)	(%)	Chi-square
Index PTH level	Mean, SD	Mean, SD	t-test
Index PTH level group			
21-64	(%)	(%)	Chi-square
65-99	(%)	(%)	Chi-square
≥100	(%)	(%)	Chi-square
Meet at least one consensus criteria for surgery?	(%)	(%)	Chi-square

Data Collection

The JDAT team at Yale New Haven Health System will extract all patient records that meet inclusion criteria in the specified time frame. A combination of data extraction from JDAT and chart review from Yale's EHR system will be used to collect data for the primary outcome, secondary objective variables and confounding variables. The US Census data will also be used to collect race data, median income data by patient zip code, and distance from home to referring facility by patient zip code.

Power Calculation

To power our study at 80%, we must observe a minimum difference in time from hypercalcemia to parathyroidectomy referral of 1.5 months with a study population of 110 per group (Appendix A). The prior study that examined racial differences in time from hypercalcemia to parathyroidectomy observed a difference much larger than 1.5 months. The study demonstrated a difference in median time from hypercalcemia to parathyroidectomy between non-Hispanic White females and Black females to be 3.22 months and 10.74 months between Black males and non-Hispanic White males. We also expect the available number of participants to be far greater than the 150 per group needed for adequate power. Mallick et al.'s study used similar inclusion criteria to our proposed study. They included 2,289 Black and non-Hispanic White patients with hypercalcemia and abnormal parathyroid hormone levels that were seen at a tertiary referral center over a 6-year time period.[4] By comparing The University of Alabama's approximately 1.6 million outpatient clinic visits a year[5] to Yale New Haven Health System's 3.6 million,[6] we estimate that our study will enroll approximately 860 patients in one year.

Given the incidence of PHPT in 2017 was estimated to be 4.03:1.37 female:male,[7] we estimate that in one year our proposed study would enroll approximately 640 females and 220 males. Given that the racial distribution of New Haven, Connecticut is approximately 30% Black people and 30% non-Hispanic White people, we estimate that the distribution of non-Hispanic White and Black patients within our sample would be even.[8] Therefore, we will enroll approximately 1700 patients over the course of the two year recruitment period with approximately 850 patients per group. Our estimated sample

size remains adequate with consideration of the number of additional participants needed to account for all confounding variables.

Analysis

Descriptive characteristics of the groups will be reported and compared as follows: age and index calcium level will be reported as mean and standard deviation and compared with the student t-test. Median income and distance from home to referring facility will be reported as median and IQI and compared with the Wilcoxon rank-sum test. Categorical characteristics will include age group, gender, highest completed education level, insurance type, income, Charlson Comorbidity Index, index PTH level group, and index calcium level group and be compared with the chi-squared test. Insurance change during study period and meeting at least one consensus criteria for surgery will be dichotomous and compared using the chi-squared test.

A bivariate analysis will be completed for the primary outcome of this study, median time from hypercalcemia to surgical referral, using Kaplan-Meier time-to-event curves. Groups will be compared with the log-rank test. Cox proportional hazards regression will be used to estimate differences in time to recurrence between non-Hispanic White and Black patients, while simultaneously adjusting for confounders listed in table 1: mean age, age group, gender, highest completed education, insurance type, insurance change during study period, median income, median income group, median distance from home to referring facility, Charlson comorbidity index group, mean index PTH, index PTH level group mean index calcium, index calcium level group, and meeting at least one surgery criteria. This analysis will then be repeated with stratification by race and gender: Black males, Black females, non-Hispanic White males, and non-Hispanic White females.

Bivariate analysis will also be completed for the secondary objective of comparing disease characteristics according to consensus surgical guidelines. Urine calcium, eGFR, CrCl and vitamin D will be reported as mean and standard deviation and compared with the student t-test. Urine calcium > 400 mg/dL, eGFR < 60 mL/min, CrCl < 60 mL/min, osteopenia, osteoporosis, nephrocalcinosis, nephrolithiasis, vertebral fracture, fragility fracture, completed work up, and referral by endocrinologist will be reported as dichotomous and compared with the chi-squared test.

All continues variables will be operationalized as parametric or non-parametric to be consistent with metrics from previous studies.

Timeline and Resources

We estimate the study to require approximately 6 months. Two months will be dedicated to record collection and review from Yale New Haven Health's databases. An additional two months will be allotted for analysis of the data and the final two months will be dedicated to finalizing a paper for publication. The study requires access to Yale Health's data extraction team, JDAT, and to Yale New Haven Health's EHR system for chart review. The primary investigator will be Dr. Patricia Peter, MD, and the co-primary investigator will be Jordan Lidsky-Everson, PA-SII.

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Chapter 4 – Conclusion

Advantages

Advantages of the retrospective study design include decreased cost, decreased time needed to conduct the study given that data is already collected, ability to examine an outcome that may take years to occur, and capacity to enroll a large amount of participants. More specifically, our study design improves on prior studies by using a more practical start point and a more consistent endpoint. Our study design will strive to capture a more accurate time from PHPT diagnosis to surgical referral than previous studies and therefore give us a better understanding of what factors may be contributing to racial disparities in time from diagnosis to treatment referral. Another advantage of our study is that it is designed to be the first study to examine the association between individual surgical criterion and time to surgical referral with racial stratification. This may help elucidate whether the presence of certain surgical criteria consistently leads to surgical referral.

Disadvantages

One disadvantage of the study design is that the quality of the data is dependent on the accuracy and consistency of documentation by providers in the EHR which is outside our control. Also, there are some variables that we are unable to capture because of EHR limitations. For example, we are unable to analyze racial disparities of nonspecific disease symptoms, such as fatigue, general malaise, irritability, depression, and memory problems, and their association with referral delay because these are not diagnoses discretely entered in the EHR but rather symptoms more likely to be written or dictated into an office note and therefore are unable to be easily extracted for analysis.

There are multiple other confounding variables that we are unable to capture due to limitations of EHR data that may affect the amount of time from diagnosis to referral

for treatment including implicit bias and trust in the healthcare system or providers. Several studies have demonstrated provider implicit bias is highest against Black patients and can lead to unequal treatment and disparities in care.[1-3] Higher medical mistrust among Black patients has also been shown to delay routine healthcare appointments, tests and treatments.[4,5] We are also unable to ascertain from examining EHR data whether Black patients experience longer delays to referral to treatment because they are refusing treatment more often than non-Hispanic White patients. It is clear that Black patients undergo parathyroidectomy less often that non-Hispanic White patients which could be related to disparities in access to care and greater travel burden.[6,7] However, multiple studies have shown that Black patients undergoing thyroidectomy and parathyroidectomy have longer postoperative lengths of stay, higher complication rates, higher mortality rates, and higher hospital costs compared to non-Hispanic White patients which may influence patient decision-making regarding surgery.[8,9] Implicit bias, medical mistrust and treatment refusal are not variables documented in the EHR in a way in which our study would be able to extract and analyze them.

The external validity of the study is limited to Black and non-Hispanic White patients who have hypercalcemic PHPT. The results cannot be applied to patients of other races or patients who have normocalcemic PHPT since our study used serum calcium above the upper limit of normal for inclusion in the study. However, normocalcemic PHPT is recognized as an alternative presentation of PHPT with many of the same disease sequelae as hypercalcemic PHPT and is estimated to make up approximately 6% of patients who undergo parathyroidectomy.[10] The results also cannot be applied to patients with stable, mild PHPT with no surgical indications. Prior studies have found the

percentage of patients that did not meet surgical criteria within their study population to be between 30% and 50%.[11,12]

Additionally, due to the retrospective nature of the study, no conclusions can be made about the causal relationship between race and delays in time to surgical referral.

Clinical and/or Public Health Significance

If a longer delay from diagnosis to surgical referral is shown to exist among Black patients with PHPT, it would support the need for more studies to determine the cause. Not only could a delay contribute to the higher disease severity seen in Black patients, but longer time to treatment means that Black patients are going without a procedure that has been shown to significantly reduce morbidity and decrease health care costs.[13-17] The results of this study could provide more information on where resources and research could be spent to most effectively reduce disparities in PHPT. The study may also improve provider awareness of potential inconsistencies or knowledge gaps in their own practices that are contributing to under recognition, underdiagnosis or under-referral for Black patients. The study is also an opportunity to examine the most recent consensus guidelines for surgery and whether alterations to the guidelines would more accurately identify patients who would benefit from surgery given that Black patients may present with different disease manifestations than non-Hispanic White patients despite the incidence of PHPT being highest among Black patients and the probability of undergoing surgery lower among Black patients.[6,7,18]

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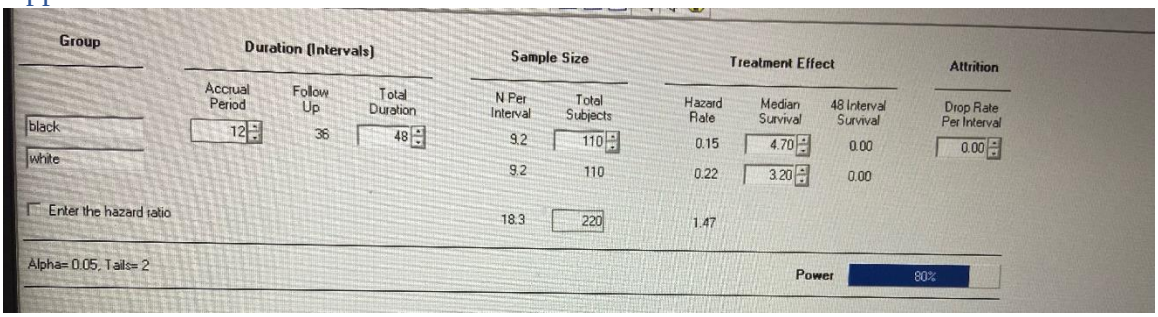
Appendices

Appendix A - Power Calculation



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