

Incidence and risk factors for development of persistent postsurgical pain following total knee arthroplasty

A retrospective cohort study

Semih Gungor, MD^{a,*}, Kara Fields, MSc^b, Rohit Aiyer, MD^c, Alejandro Gonzalez Della Valle, MD^d, Edwin P. Su, MD^d

Abstract

Persistent postsurgical pain (PPP) is defined as the discomfort that lasts >3 months postoperatively. The primary aim of this retrospective study was to estimate the risk of developing moderate-to-severe PPP after primary total knee arthroplasty (TKA). The secondary goal was to explore potential predictors of this outcome.

Data were collected via hospital arthroplasty registry and chart review. The risk of moderate-to-severe PPP, defined as ≥ 4 on the numerical rating scale (NRS) at minimum of 3 months post-surgery, was calculated. Multivariable logistic regression was used to estimate the association of patient demographics, diagnoses, length of hospital stay, and preoperative NRS with the odds of developing PPP. Exploratory, simple logistic regression was used to estimate the association of perioperative factors with the odds of developing PPP on a subset of patients ($n=72$).

The risk of PPP after TKA was 31.3% (95% confidence interval [CI]: 27.5–35.0) ($n=578$). Every 2-point increase in baseline NRS was associated with 1.66 (95% CI: 1.37–2.03) times the odds of developing PPP ($P < .001$). African-Americans (vs whites) had 1.82 (95% CI: 1.03–3.22) times the odds of developing PPP ($P = .040$). Exploratory analysis suggested that the adductor canal saphenous nerve (vs femoral nerve) blocks were associated with 2.87 (95% CI: 1.00–8.26) times the odds of developing PPP ($P = .049$).

This study estimated a high risk (31.3%) of moderate-to-severe PPP after primary TKA. This study suggested that higher preoperative pain scores might be associated with greater odds of developing PPP. Moreover, this study suggested the possibility that racial differences and types of peripheral nerve blocks might be associated with greater odds of developing moderate-to-severe PPP after TKA surgery. However, the evidence obtained from our exploratory analysis of limited data certainly requires further exploration in large-scale studies.

Abbreviations: ACB = adductor canal block, BMI = body mass index, FNB = femoral nerve block, IASP = International Association for Study of Pain, NRS = Numeric Rating Scale, PNB = peripheral nerve block, PPP = persistent postsurgical pain, TKA = total knee arthroplasty.

Keywords: analgesia, chronic pain, complication, knee arthroplasty, nerve block, persistent postoperative pain

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^a Department of Anesthesiology, Division of Pain Medicine, Hospital for Special Surgery, Weill Cornell Medicine, ^b Healthcare Research Institute, Hospital for Special Surgery, ^c Department of Anesthesiology, ^d Department of Orthopedic Surgery, Hospital for Special Surgery, Weill Cornell Medicine, New York, New York.

* Correspondence: Semih Gungor, Department of Anesthesiology, Division of Pain Medicine, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021 (e-mail: gungors@hss.edu).

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1. Introduction

Total knee arthroplasty (TKA) is a common procedure performed to improve the pain and disability secondary to end-stage knee arthritis when nonsurgical management is no longer effective.^[1] However, a significant number of patients undergoing TKA develop disabling long-term postoperative pain despite unremarkable physical examinations and diagnostic studies.^[2] Persistent postsurgical pain (PPP) is defined by The International Association for Study of Pain (IASP) as the discomfort that lasts for >3 months after surgery.^[3] It is estimated that 10% to 44% of TKA patients develop PPP,^[4–6] with the highest-quality studies reporting an incidence of approximately 20%.^[4]

The economic impact of long-term, moderate-to-severe, and unexplained pain after TKA is profound.^[7] Therefore, preoperative identification of the patients at risk and implementation of better preventive strategies may help to reduce the incidence of PPP and improve outcomes.^[8,9]

The primary aim of this retrospective study was to estimate the risk of developing moderate-to-severe PPP after primary TKA,

defined as a score of ≥ 4 on the 11-point numerical rating scale (NRS) at a minimum of 3 months postoperatively. The secondary goal was to explore potential predictors of the development of PPP in this clinical setting.

2. Materials and methods

This retrospective cohort study was approved by the Institutional Review Board (IRB#2015–0167) and was designed to estimate the risk of moderate-to-severe PPP after TKA in a single center specializing in the treatment of musculoskeletal diseases. Data from the IRB-approved Legacy Registry and Collaborative Orthopedic Replacement Registry (CORRe) at the Hospital for Special Surgery were used for this retrospective analysis. The requirement for written consent was waived by the IRB.

Eligibility criteria required patients to have had unilateral or bilateral primary TKA performed between January 3, 2011 and April 13, 2015 recorded in the CORRe registry. Exclusion criteria included >1 operating room admission during the study period, incomplete demographic information, TKA for a reason other than osteoarthritis or inflammatory arthritis, and incomplete NRS data. NRS data were considered complete if the patient had a preoperative score and at least 1 score at minimum of 3 months postoperatively. Data collected from the CORRe and Legacy registries included NRS pain scores (preoperative and 3, 6, and 12 months postoperative), demographics (age, sex, race, American Society of Anesthesiologists [ASA] status), comorbidities (hypertensive disease, ischemic heart disease, pulmonary disease, chronic kidney disease, diabetes mellitus, mood disorder, anxiety disorder, tobacco use), reason for surgery (osteoarthritis vs inflammatory arthritis), laterality (simultaneous bilateral vs unilateral TKA), and length of hospital stay. Comorbidities and reason for surgery were determined via *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis codes. Chart review was used to obtain preoperative opioid use, tourniquet duration, peripheral nerve block (PNB) type, and perioperative gabapentinoid use for the subset of patients with NRS pain scores available in the database.

Total of 8149 TKA cases were identified between January 3, 2011 and April 13, 2015. A total of 5981 patients had single operating room visit and complete demographic information. A total of 5949 patients underwent TKA for osteoarthritis or inflammatory arthritis. A total of 1172 patients had the preoperative NRS score available in the registry database. Five-hundred seventy-eight patients had minimum ≥ 3 -month (up to 12-month) postoperative NRS scores available in the registry database (Fig. 1).

We reviewed the entire data in the registry database during the study time period without any selection bias. Data collectors were blinded to NRS pain scores and were not involved in the data analysis or manuscript preparation.

2.1. Statistical analysis

2.1.1. Sample size calculation. Assuming a 20% to 40% risk of developing PPP^{4–6} at 95% Wilson score confidence interval with ($\pm 2\%$) precision, an estimated sample size of 1535 to 2300 patients would be required respectively. We were able to identify 578 patients with the complete data available for our study in the registry database. We analyzed the data for 578 patients, which were less than the estimated sample size, but still had validity from the statistical point of view, indicating that the calculated

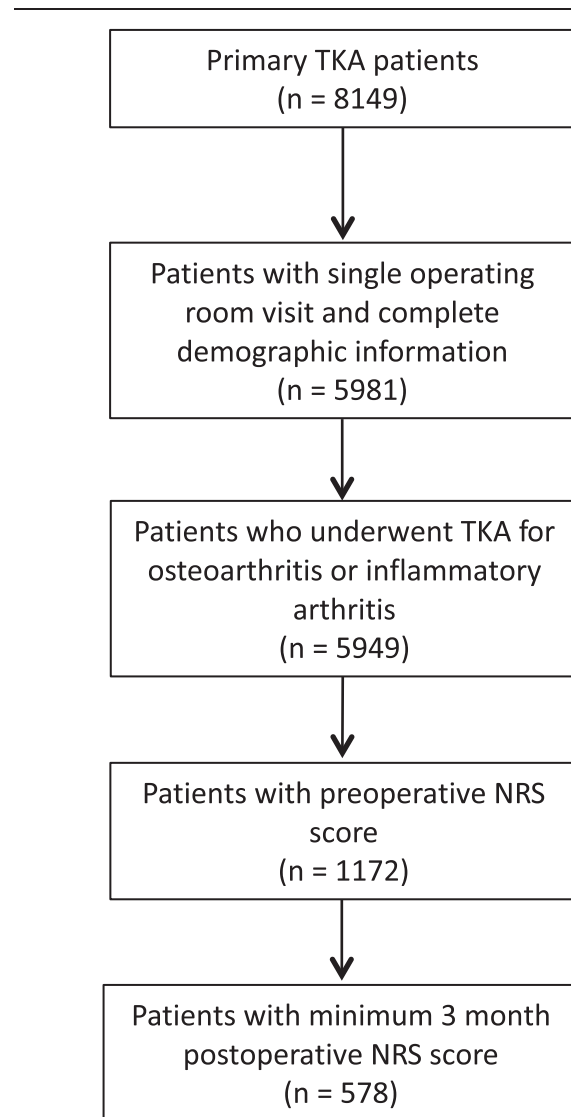


Figure 1. The patient selection flow diagram.

result would be less precise than projected. Henceforth, assuming a 20% to 40% risk of developing PPP with a sample size of 578, at 95% Wilson score confidence interval, the estimation precession is $\pm 4\%$, as opposed to the anticipated $\pm 2\%$.

2.1.2. Statistical methods. Continuous variables are summarized as means with standard deviations (SD) or medians with 1st and 3rd quartiles. Categorical variables are summarized as frequencies and percentages. Continuous variables were compared between patients with and without preoperative NRS pain scores using 2-sample *t* tests or Wilcoxon rank-sum tests, depending upon the distribution of the data. Categorical variables were compared between patients with and without preoperative NRS pain scores using χ^2 , Fisher exact, or Cochran-Armitage trend test, as appropriate. The risk of moderate-to-severe PPP is presented as a point estimate with 95% Wilson score confidence interval. The association between 18 a priori selected predictors and the odds of developing moderate-to-severe PPP was assessed using a Firth's penalized multivariable logistic regression model. Variance inflation factor test was

Table 1
Patient and surgery characteristics.

Variable	At least 3-month follow-up (n=578)	<3-month follow-up (n=594)	P
Preoperative NRS pain score, mean ± SD	7.2 ± 2.2	7.3 ± 2.2	.302
Age, y, mean ± SD	66.0 ± 9.3	66.1 ± 9.9	.968
Female, n (%)	216 (37.4)	241 (40.6)	.261
Race, n (%)			.250
White	491 (84.9)	523 (88.0)	
Black	65 (11.2)	50 (8.4)	
Other	22 (3.8)	21 (3.5)	
ASA status, n (%)			.0360
1	12 (2.1)	12 (2.0)	
2	486 (84.1)	470 (79.1)	
3	80 (13.8)	112 (18.9)	
Hypertensive disease, n (%)	328 (56.7)	342 (57.6)	.775
Ischemic heart disease, n (%)	47 (8.1)	68 (11.4)	.056
Pulmonary circulation disease, n (%)	15 (2.6)	16 (2.7)	.916
Chronic kidney disease, n (%)	13 (2.2)	19 (3.2)	.319
Diabetes mellitus, n (%)	84 (14.5)	73 (12.3)	.260
Mood disorder, n (%)	65 (11.2)	59 (9.9)	.465
Anxiety disorder, n (%)	66 (11.4)	65 (10.9)	.796
Tobacco use, n (%)	16 (2.8)	30 (5.1)	.044
Reason for surgery, n (%)			.393
Osteoarthritis	553 (95.7)	574 (96.6)	
Inflammatory Arthritis	25 (4.3)	20 (3.4)	
Simultaneous bilateral surgery, n (%)	116 (20.1)	85 (14.3)	.009
Length of hospital stay, median (Q1, Q3)	5 (4, 5)	5 (4, 5)	.009

ASA=American Society of Anesthesiologists, NRS=Numeric Rating Scale, SD=standard deviation. Minimum 3-month postoperative NRS pain score follow-up.

performed, and no multicollinearity problem was detected. Normality of distribution was determined by Shapiro-Wilk testing wherein significance of $>.05$ indicates normally distributed data. For the subgroup of patients with NRS pain scores available at all time points (preoperative, 3 months, 6 months, and 12 months; $n=72$), additional data were collected. Given the small size of this subgroup, separate simple logistic regression models were used to explore the association between each predictor and the odds of developing PPP. Statistical analyses were performed with SAS Version 9.3 (SAS Institute, Cary, NC).

3. Results

The patient selection flow diagram is shown in Figure 1. Patients with and without minimum a 3-month postoperative NRS pain score were mostly similar with respect to baseline NRS pain scores, demographics, and comorbidities. Exceptions included that patients with postoperative follow-up data had better ASA status, were less likely to use tobacco, more likely to have had simultaneous bilateral TKA, and had slightly longer lengths of hospital stay (Table 1).

The risk of moderate-to-severe PPP after primary TKA was calculated as 31.3% (95% confidence interval [CI]: 27.5–35.0).

Multivariable logistic regression revealed associations between baseline NRS pain score and the odds of developing moderate-to-severe PPP (Table 2). Specifically, every 2-point increase in baseline NRS pain score was associated with 1.66 (95% CI: 1.37–2.03) times the odds of developing moderate-to-severe PPP ($P < 0.001$).

Regression also suggested an association between race and the odds of developing moderate-to-severe PPP. African-American patients had 1.82 (95% CI: 1.03–3.22) times the odds of

developing persistent postoperative pain compared to white patients ($P = .040$) (Table 2).

There was no evidence of an association between mood disorders and the odds of developing moderate-to-severe PPP ($P = .465$) (Table 2).

Exploratory, simple logistic regression analyses suggested that adductor canal blocks (ACB) may be associated with greater odds of developing moderate-to-severe PPP than femoral blocks when used for postoperative analgesia ($P = .049$) (Table 3). Tourniquet duration and perioperative gabapentinoid use were not associated with the odds of developing moderate-to-severe PPP ($P = .728$ and $P = .921$, respectively) (Table 3).

4. Discussion

A Numeric Rating Scale (NRS) score of ≥ 4 is considered as moderate-to-severe pain, and is recommended as a trigger for a more comprehensive assessment and treatment.^[10] Previous studies in this area of research have reported that approximately 25% of patients had complaints of significant pain (equivalent to NRS >4) at 3 months after TKA, despite normal clinical evaluation and radiographic work-up,^[2] and the incidence of chronic pain was $\geq 20\%$ at 3 to 24 months postoperatively.^[11] In one study, up to 44% of TKR patients reported PPP of any severity.^[6]

Some of the causes of long-term postsurgical pain after TKA include: mechanical pain secondary to poor prosthetic design and positioning, component loosening, periprosthetic fractures, ligament imbalances, patellofemoral disorders; inflammatory pain, which may occur due to a prolonged inflammatory response for implanted prosthesis or infection, and 3) neuropathic pain that arises after nerve injuries and sensitization of pain pathways.^[3,12–14]

Table 2

Multivariable logistic regression model of moderate-to-severe persistent postoperative pain at least 3 months after the surgery. The patient was categorized as having PPP if NRS ≥ 4 at any of the 3 time-points (3, 6, 12 months).

Predictor	NRS ≥ 4 (n = 180)	NRS < 4 (n = 398)	Adjusted odds ratio (95% CI)	P
Preoperative NRS pain score (per 2 points), mean \pm SD	7.9 \pm 1.9	6.8 \pm 2.2	1.66 (1.37–2.03)	<.001
Age (per 10 y), mean \pm SD	64.9 \pm 9.8	66.6 \pm 9.0	0.84 (0.68–1.04)	.117
Female vs male, n (%)	116 (64.4)	246 (61.8)	0.97 (0.65–1.45)	.876
Race, n (%)				
Black vs white	31 (17.2)	34 (8.5)	1.82 (1.03–3.22)	.040
Other vs white	9 (5.0)	13 (3.3)	1.86 (0.73, 4.74)	.194
ASA–n (%)				
1 vs 2	6 (3.3)	6 (1.5)	2.92 (0.84, 10.13)	.063
3 vs 2	25 (13.9)	55 (13.8)	0.75 (0.41–1.36)	.060
Hypertensive disease, n (%)	105 (58.3)	223 (56.0)	1.01 (0.68–1.5)	.978
Ischemic heart disease, n (%)	15 (8.3)	32 (8.0)	1.27 (0.61–2.65)	.530
Pulmonary circulation disease, n (%)	5 (2.8)	10 (2.5)	0.86 (0.27–2.79)	.806
Chronic kidney disease, n (%)	2 (1.1)	11 (2.8)	0.52 (0.12–2.36)	.399
Diabetes mellitus, n (%)	33 (18.3)	51 (12.8)	1.53 (0.9–2.6)	.114
Mood disorder, n (%)	22 (12.2)	43 (10.8)	1.04 (0.58–1.88)	.886
Anxiety disorder, n (%)	26 (14.4)	40 (10.1)	1.57 (0.89–2.76)	0.121
Tobacco use, n (%)	5 (2.8)	11 (2.8)	0.93 (0.3–2.9)	.901
Inflammatory arthritis vs osteoarthritis, n (%)	6 (3.3)	19 (4.8)	0.56 (0.21–1.49)	.242
Simultaneous bilateral surgery, n (%)	32 (17.8)	84 (21.1)	0.64 (0.38–1.06)	.081
Length of hospital stay, median (Q1, Q3)	5 (4, 6)	5 (4, 5)	1.15 (0.99–1.35)	.076

CI = confidence interval, ASA = American Society of Anesthesiologists, NRS = Numeric Rating Scale.

We used the IASP definition of PPP, defined as a NRS score ≥ 4 at minimum of 3 months post-surgery.^[3] Our analysis of the available registry data showed that the incidence of PPP after primary TKA was 31.3% (95% CI: 27.5–35.0).

Although our estimate of the risk of PPP in primary TKA patients was within the range of other results reported in the literature,^[4,6,14–16] the results should be interpreted with caution because of some of the limitations of present study; in our sample, the number of patients with complete data was less than estimated (N = 578 instead of 1535 for 20% risk and 2300 for 40% risk of developing PPP). Therefore, our estimate of the persistent postoperative pain risk was less precise than projected (ie, a precision of $\pm 4\%$ as opposed to the anticipated $\pm 2\%$). There is also a possibility of overestimation, likely attributable to follow-up bias. It is possible that patients with PPP were more likely to return for a follow-up visit and report NRS scores than those without PPP. Our registry database did not include the amount of analgesic medication use after 3 months postoperatively. Therefore, the patients who were actively taking analgesic medications and reported their pain levels as low (NRS < 4) at 3-, 6-, and 12-month time points were not included in our analysis.

This might have led to underestimation of our calculated result of risk of PPP development after TKA.

Preoperative identification of high-risk patients and the implementation of better preventive strategies including patient education, analgesia, and physical therapy may serve as a strategy to reduce poor outcomes after TKA.^[2,8,9] In one meta-analysis, it was reported that variables such as severe baseline preoperative pain and catastrophizing were the strongest independent predictors for development of PPP after TKA.^[8] Our analysis showed that every 2-point increase in baseline NRS was associated with 1.66 (95% CI: 1.37–2.03) times the odds of developing PPP ($P < .001$). Our results were consistent with other studies reported in the literature in that the baseline preoperative pain score was an important predictor of increased risk for development of PPP. There is evidence that sensitization of pain pathways owing to severe uncontrolled preoperative pain may play a role in the development of neuropathic pain in osteoarthritic knee, in addition to mechanical and inflammatory pain.^[17] This may be one of the possible explanations by which the incidence of PPP increases if patients present with higher baseline preoperative pain levels before TKA surgery.

Table 3

Simple logistic regression models of moderate-to-severe persistent postoperative pain in a subgroup of 72 patients with pain data at all time points.

Predictor	NRS ≥ 4		NRS < 4		Crude odds ratio (95% CI)	P
	N		N			
Preoperative oral opioids, n (%)	31	6 (19.4)	41	6 (14.6)	1.39 (0.40–4.82)	.602
Tourniquet duration (per 10 min), median (Q1, Q3)	31	47 (37, 55)	41	50 (38, 55)	0.95 (0.69–1.29)	.728
Femoral vs saphenous PNB, n (%)	31	17 (54.8)	37	29 (78.4)	0.35 (0.12–1.00)	.049
Perioperative gabapentinoids, n (%)	31	10 (32.3)	40	13 (32.5)	0.99 (0.36–2.69)	.983

CI = confidence interval, ASA = American Society of Anesthesiologists, NRS = Numeric Rating Scale, PNB = peripheral nerve block.

In our study, African-American race was associated with 1.82 (95% CI: 1.03–3.22) times the odds of developing PPP compared to white patients ($P=.040$). There is conflicting and limited evidence regarding this topic in the medical literature. Although one meta-analysis reported that racial background had limited influence on predictors of persistent pain at >3 months after TKA,^[8] there were studies indicating that African-Americans had higher rates of pain scores when compared to other races.^[18–20] Our study was limited to only 65 patients who reported their racial background as African-American in our data sample (white=513 vs African-American=65). Therefore, the authors of this manuscript believe that further studies are required to better explore racial differences in the development of PPP after TKA.

A total of 68 patients included in our sample analysis with 46 patients were given femoral nerve block (FNB) and 22 patients were given ACB for adjunct postoperative analgesia. The majority of the patients in our dataset had combined spinal-epidural anesthesia, with continuation of the epidural catheter for postoperative analgesia through the first postoperative day, along with adjunct postoperative analgesia using either FNB or ACB performed before surgical incision.

Interestingly, our exploratory simple logistic regression analyses suggested that ACB might be associated with higher odds of developing persistent postoperative pain than FNB ($P=.049$).

Review of literature in regards to relationship of ACB and nerve injury showed one study that was designed to determine the risk of saphenous nerve injury in postoperative TKA patients when ACB is also used for analgesia.^[21] This study did not specifically question PPP, but only tested the sensory abnormalities in certain areas of the operated limb 3 months postoperatively. Their conclusion was that the sensory changes were frequent, but mostly confined to the distribution of the infrapatellar branch of the saphenous nerve, which has a known anatomical susceptibility to injury during TKA. The cutaneous area innervated by the medial crural branch of the saphenous nerve on the leg was relatively spared. This study concluded that a serious risk of nerve injury related to ACB was unlikely,^[21] which was not consistent with our findings of potentially increased PPP with ACB. Therefore, the authors of this manuscript believe that further studies are required to better explore risks associated with peripheral nerve blocks in the development of PPP after TKA.

Multivariable logistic regression analysis of our entire sample did not detect an association of mood or anxiety disorders with the odds of developing persistent postoperative pain ($P=.886$ and $.121$, respectively). Simple logistic regression analyses on a subsample of patients ($N=72$) did not detect an association of perioperative gabapentinoid use or tourniquet duration with the odds of developing persistent postoperative pain ($P=.921$ and $.728$, respectively).

4.1. Limitations

This was a retrospective review of data from a limited time period at a single institution. In our sample, the number of patients with complete data was less than estimated ($N=578$ instead of 1535 and 2300, for 20% and 40% risk of developing PPP respectively). Therefore, our estimate of the persistent postoperative pain risk was less precise than projected (ie, a precision of $\pm 4\%$ as opposed to the anticipated $\pm 2\%$). There is also a possibility of overestimation, likely attributable to follow-up bias. It is possible

that patients with PPP were more likely to return for a follow-up visit and report NRS scores than those without PPP.

Our registry database did not include the amount of analgesic medication use after 3 months postoperatively. Therefore, the patients who were actively taking analgesic medications and reported their pain levels as low (NRS <4) at 3-, 6-, and 12-month time points were not included in our analysis. This might have led to underestimation of our calculated result of risk of PPP development after TKA. Also, we did not have the data for various validated tests to differentiate the pain types as neuropathic versus other types in the registry database. As the data about the body mass index of patients and acute postoperative pain scores were inadequate in the orthopedic registry database, these items could not be included in our retrospective analysis.

5. Conclusions

This study estimated a high risk (31.3%) of moderate-to-severe PPP development in patients undergoing primary TKA from a sample of 578 patients. This study suggested that higher preoperative pain scores may be associated with greater odds of developing moderate-to-severe PPP after TKA surgery.

Moreover, this study suggested the possibility that racial differences and types of peripheral nerve blocks might be associated with greater odds of developing moderate-to-severe PPP after TKA surgery. However, the evidence obtained from our exploratory analysis of limited data certainly requires further exploration in large-scale studies.

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Author contributions

Conceptualization: Semih Gungor, Alejandro Gonzalez DellaValle, Edwin Su.

Data curation: Kara Fields.

Formal analysis: Semih Gungor, Kara Fields.

Investigation: Semih Gungor, Rohit Aiyer.

Methodology: Semih Gungor.

Project administration: Semih Gungor.

Resources: Semih Gungor, Kara Fields, Alejandro Gonzalez DellaValle, Edwin Su.

Software: Semih Gungor, Kara Fields, Rohit Aiyer, Alejandro Gonzalez DellaValle, Edwin Su.

Supervision: Semih Gungor.

Validation: Semih Gungor, Kara Fields.

Writing – original draft: Semih Gungor, Kara Fields, Rohit Aiyer.

Writing – review & editing: Semih Gungor, Kara Fields, Rohit Aiyer, Alejandro Gonzalez DellaValle, Edwin Su.

Semih Gungor orcid: 0000-0002-4484-9183.

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