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Risk factors for persistent post-surgical pain after tibia fracture: a longitudinal study

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Abstract

Background: Although persistent post-surgical pain after tibia fracture is common, its predictors have received limited study. **Purposes:** We used data collected as part of the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) to address, among patients with a tibial shaft fracture, the association between baseline characteristics and persistent pain up to 12 months post-operatively. **Patients and Methods:** Patients were adults with an open or closed tibial fracture enrolled in TRUST at 43 participating centers across Canada and the United States between October 2008 and September 2012. We defined our study outcome, the resolution of troublesome pain, as no more than mild persistent pain (pain score ≤3 on a 0-10 Numeric Rating Scale) at two consecutive follow-up visits. We used a multivariable Cox proportional hazards regression model for analysis. **Results:** We included 481 patients with open or closed fractures of the tibia who underwent surgical repair. During the 12-month follow-up period, 313 of 481 (65.1%) participants reported resolution of troublesome pain. We found significant independent associations between resolution of troublesome pain and male sex (hazard ratio [HR]=1.34 [95% confidence interval (CI), 1.04 to 1.72]), non-smoking (HR=1.74 [95% CI, 1.33 to 2.29]) and alcohol consumption (HR=1.35 [95% CI, 1.06 to 1.73]). Age, obesity, type of fracture (closed versus open), additional injuries, and post-operative weight-bearing status did not predict resolution of troublesome pain. **Conclusions:** In our study, non-medical factors were predictive of persistent troublesome pain after tibial fracture repair, whereas injury severity was not. Results of the study will alert clinicians of the higher risk of persistent post-operative troublesome pain in female smokers who do not use alcohol, and allow them to use this information as a means to counsel female smokers to discontinue smoking. Further prospective studies are needed to confirm or refute the findings in our study.

Keywords: Persistent pain, Post-surgery, Tibial shaft fracture, Predictor.

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INTRODUCTION

Tibia fractures are the most frequent type of long bone fracture [1-3]. The National Center for Health Statistics reported 492,000 tibia fractures per year in the United States [3]. Tibia fractures often require prolonged rehabilitation or multiple operative procedures to achieve maximal functional recovery.

Persistent post-surgical pain (PPSP), defined in the 11th version of the International Classification of Diseases of the World Health Organization (WHO) as pain that lasts for at least three months after a surgical procedure excluding other causes of pain [4-6], is common amongst patients who undergo surgery following

lower extremity fractures [7]. Greater duration and severity of post-surgical pain is associated with less mobility [8], restrictions in activities of daily living, and reduced quality of life [1,3,9-11].

Although PPSP after fracture repair is common, predictors of persistent pain have received limited study. Therefore, we conducted a longitudinal study to assess the association between patients' characteristics and PPSP in adults with tibial fracture up to 12 months postoperatively.

METHODS

Study Design and Participants

The current study used data collected as part of a large, prospective, multi-center randomized controlled trial, the Trial to Re-evaluate Ultrasound in the Treatment of Tibial Fractures (TRUST) [12,13]. The TRUST Investigators (Appendix 1) evaluated the impact of low-intensity, pulsed ultrasound applied to tibial shaft fractures treated with intramedullary nailing on functional status, time to radiographic healing of fractures and rates of nonunion. The trial enrolled adults aged 18 years or older, with an open or closed tibial fracture amenable to intramedullary nail fixation seen at 43 participating centers across Canada and the United States between October 2008 and September 2012 (last assessment April 2013, data of last contact in May 2013). The trial found no benefit of the Sonic Accelerated Fracture Healing System (SAFHS®) device applied within 14 days of fracture nailing treatment versus placebo [12,13].

The McMaster University Research Ethics Board and local ethics boards at each participating site approved the TRUST protocol (REB #08-171). All participants provided written informed consent prior to participation. The TRUST pilot study [12] and the TRUST definitive trial [13] have been published elsewhere.

Measurement of PPSP

Patients were evaluated prior to surgery and at 6, 12, 18, 26, 32, 38, 44 and 52 weeks after surgical repair of their tibia fractures. At each of these visits, patients rated their level of pain intensity on a 0-10 Numeric Rating Scale, with 0 representing no pain and 10 representing the worst pain possible.

Definition of outcome - Resolution of troublesome pain

In the current study, we defined PPSP as pain persisting either continuously or intermittently for 3 months or more after surgery [4-6]. We defined our study outcome, the resolution of troublesome pain, as a patient report of mild or no pain (pain score ≤3) [14,15] at two consecutive follow-up visits, and pain score would not increase beyond 3 anymore.

Independent Variables

We present continuous variables as means and standard deviations and categorical and binary variables as proportions. Orthopedic surgeons and pain researchers (MB, JWB, BP and GG) identified the following possible predictors of post-operative pain: age, sex, body mass index (BMI), smoking status, alcohol use, diabetes, kidney disease or renal insufficiency, vascular disease, rheumatoid arthritis, co-morbidity requiring chronic steroid use, fracture type (open from Gustilo type I-IIIB or closed from Tscherne grade 0-3), whether there were additional injuries, intramedullary nailing with or without reaming, and post-operative weight-bearing status on the day of surgery (non, partial or full). The identified variables were independent from each other from clinical perspectives.

Based on the standard BMI cutoff points that the WHO has recommended for classification of obesity (≥30 kg/m^2) [16], we categorized BMI into two groups: 1) non-obese (BMI <30 kg/m^2) and 2) obese (BMI ≥30 kg/m^2). We also categorized post-operative weight-bearing status into two groups: 1) non weight-bearing and 2) partial or full weight-bearing.

Statistical Analysis

Before entering the potential prognostic factors into the multivariable models, we examined all pair-wise correlations by calculating the *r* index, considering the threshold of highly correlated to be > 0.7 [17]. For binary and categorical variables we looked at Phi or Cramer's V statistics; for continuous variables we looked at Pearson's correlation coefficient; and for continuous and categorical variables we looked at Point-Biserial correlation or the correlation coefficient from the R-square from of the ANOVA analysis [17]. For variables with correlations over 0.7, we planned to include only the variables that we considered most likely to be predictive of persistent troublesome pain. We also excluded variables in which there were less than 10 events in each of the groups with or without the presence of the putative predictor [18]. To determine the 12-month association between possible predictors and resolution of troublesome pain, we conducted a time-to-event analysis by including all other pre-specified variables in a multivariable Cox proportional hazards regression model [19,20] and tested the model to ensure the proportional hazard assumption was met. We consulted the orthopedic surgeon (BP) for any postulated interactions prior to analysis.

We report the number of participants and proportions at their last follow-ups. We look at the distribution of duration of follow-up in those who had persistent troublesome pain. We report all association estimates as hazard ratios (HRs) and 95% confidence intervals (CIs). All calculated P-values are two-tailed, with the criterion for statistical significance set at 0.05. We calculated the pair-wise correlations for variables using SAS version 9.4 (SAS Institute Inc., NC, USA) and performed the remaining analyses using SPSS version 24.0 (IBM Corp., NY, USA).

RESULTS

Of 501 patients enrolled in the TRUST study, two did not have any records of pain measurement, and 18 had only a baseline record of pain measurement. The remaining 481 patients, all of whom had data available for pain scores at least three months after surgery, were included in the analysis. Table 1 summarizes the characteristics of these 481 patients. No participants had kidney disease or renal insufficiency, vascular disease or rheumatoid arthritis. There were fewer than 10 events in each of the groups of diabetes, a comorbidity requiring chronic steroid use and type of fixation (Table 1). Fracture location (proximal, proximal-middle, middle, distal-middle and distal) was a factor highly correlated with the most plausible injury severity factor of open versus closed fracture from clinical perspective. We therefore did not consider any of these potential predictors of troublesome post-operative pain further.

We were able to follow the majority of patients (301/481, 62.6%) for the full 12 months post-surgery. Of the 481 participants, 313 (65.1%) experienced resolution of troublesome pain over 12 months.

Resolution of troublesome pain was related to duration of follow-up. The greatest reduction in the proportion experiencing troublesome pain occurred between 18 and 26 weeks of follow-up. For those followed for 26 weeks or more, there was little difference in the proportion with persistent troublesome pain (Table 2, Figure 1). If one considers only those followed for 26 weeks or more, 297/402 patients (73.9%) achieved resolution of persistent troublesome pain.

No two variables were correlated with one another at the threshold value of 0.7 or higher.

Table 1: Baseline characteristics of study participants

	Total	Resolution of troublesome pain	Persistent troublesome pain
	N (% in column)	N (% in row)	N (% in row)
Total	481 (100)	313 (65.1)	168 (34.9)
Age (years)	37.9 (14.0) *	38.7 (14.5) *	36.3 (12.8) *
Sex			
Male	331 (68.8)	217 (65.6)	114 (34.4)
Female	150 (31.2)	96 (64.0)	54 (36.0)
BMI†			
<30	349 (73.5)	222 (63.6)	127 (36.4)
≥30	126 (26.5)	85 (67.5)	41 (32.5)
Smoking			
No	330 (68.6)	236 (71.5)	94 (28.5)
Yes	151 (31.4)	77 (51.0)	74 (49.0)
Alcohol consumption			
Yes	317 (65.9)	210 (66.2)	107 (33.8)
No	164 (34.1)	103 (62.8)	61 (37.2)
Diabetes§			
No	453 (94.4)	294 (64.9)	159 (35.1)
Yes	27 (5.6)	18 (66.7)	9 (33.3)
Comorbidity requiring chronic steroid use¶			
No	471 (98.1)	306 (65.0)	165 (35.0)
Yes	9 (1.9)	6 (66.7)	3 (33.3)
Type of fracture			
Closed	371 (77.1)	252 (67.9)	119 (32.1)
Open	110 (22.9)	61 (55.5)	49 (44.5)
Location of fracture**			
Proximal	6 (1.2)	2 (33.3)	4 (66.7)
Proximal-middle	12 (2.5)	8 (66.7)	4 (33.3)
Middle	98 (20.4)	59 (60.2)	39 (39.8)
Distal-middle	264 (54.9)	166 (62.9)	98 (37.1)
Distal	114 (23.7)	82 (71.9)	32 (28.1)
Additional injuries			
No	71 (14.8)	47 (66.2)	24 (33.8)
Yes	410 (85.2)	266 (64.9)	144 (35.1)
Type of fixation ††			
Nail with prior reaming	478 (99.6)	311 (65.1)	167 (34.9)
Nail without prior reaming	2 (0.4)	2 (100)	0 (0)
Post-operative weight-bearing status on the day of surgery			
Full or partial weight-bearing	264 (54.9)	174 (65.9)	90 (34.1)
Non-weight bearing	217 (45.1)	139 (64.1)	78 (35.9)

Notes:
* Mean and standard deviation
† n=475 (349 and 126); BMI: body mass index. BMI<30: overweight, normal weight and underweight; BMI≥30: obese
§ n=480 (453 and 27)
¶ n=480 (471 and 9)
** Categories not mutually exclusive.
†† n=480 (478 and 2)

In the multivariable Cox survival regression, we found significant independent associations between resolution of troublesome pain and male sex (HR=1.34, 95% CI 1.04 to 1.72; p value=0.02), non-smoking (HR=1.74, 95% CI, 1.33 to 2.29; p value < 0.001) and alcohol consumption (HR=1.35, 95% CI, 1.06 to 1.73; p value=0.02). We did not find significant associations between persistent troublesome pain and age, obesity, type of fracture (closed versus open), additional injuries or post-operative weight-bearing status (Table 3, Figure 2). In every case, we found no violation of the proportional hazards assumption. The surgeon did not have concerns about any postulated interactions.

Table 2: Distribution of duration of participants' follow-ups among patients with persistent, troublesome post-operative pain (≥12 weeks, absolute number of patients)

	Total	Patients with persistent troublesome pain	
	N	N	(%)
Total	452	139	
12 weeks	24	15	(62.5)
18 weeks	26	19	(73.1)
26 weeks	51	17	(33.3)
32, 38 and 44 weeks	50	11	(22.0)
52 weeks	301	77	(25.6)

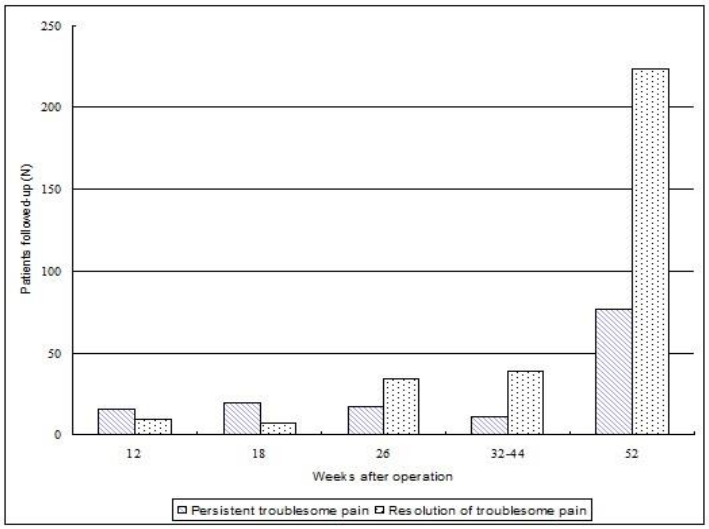

Figure 1: Distribution of duration of participants' follow-ups (≥12 weeks, absolute number of patients)

Table 3: Predictors of resolution of troublesome post-operative pain in study participants (Cox survival model, adjusted analysis)

	Hazard Ratio (95% Confidence Interval)	P value
Total		
Age, per 10 years	1.04 (0.96-1.13)	0.36
Sex		
Male	**1.34 (1.04-1.72)**	**0.02**
Female	1.00	
BMI*		
<30	1.03 (0.80-1.32)	0.83
≥30	1.00	
Smoking		
No	**1.74 (1.33-2.29)**	**<0.001**
Yes	1.00	
Alcohol consumption		
Yes	**1.35 (1.06-1.73)**	**0.02**
No	1.00	
Type of fracture		
Closed	1.12 (0.84-1.49)	0.45
Open	1.00	
Additional injuries		
No	0.90 (0.65-1.24)	0.50
Yes	1.00	
Post-operative weight-bearing status on the day of surgery		
Full or partial weight-bearing	1.12 (0.88-1.41)	0.36
Non-weight bearing	1.00	

Note:
* BMI: body mass index

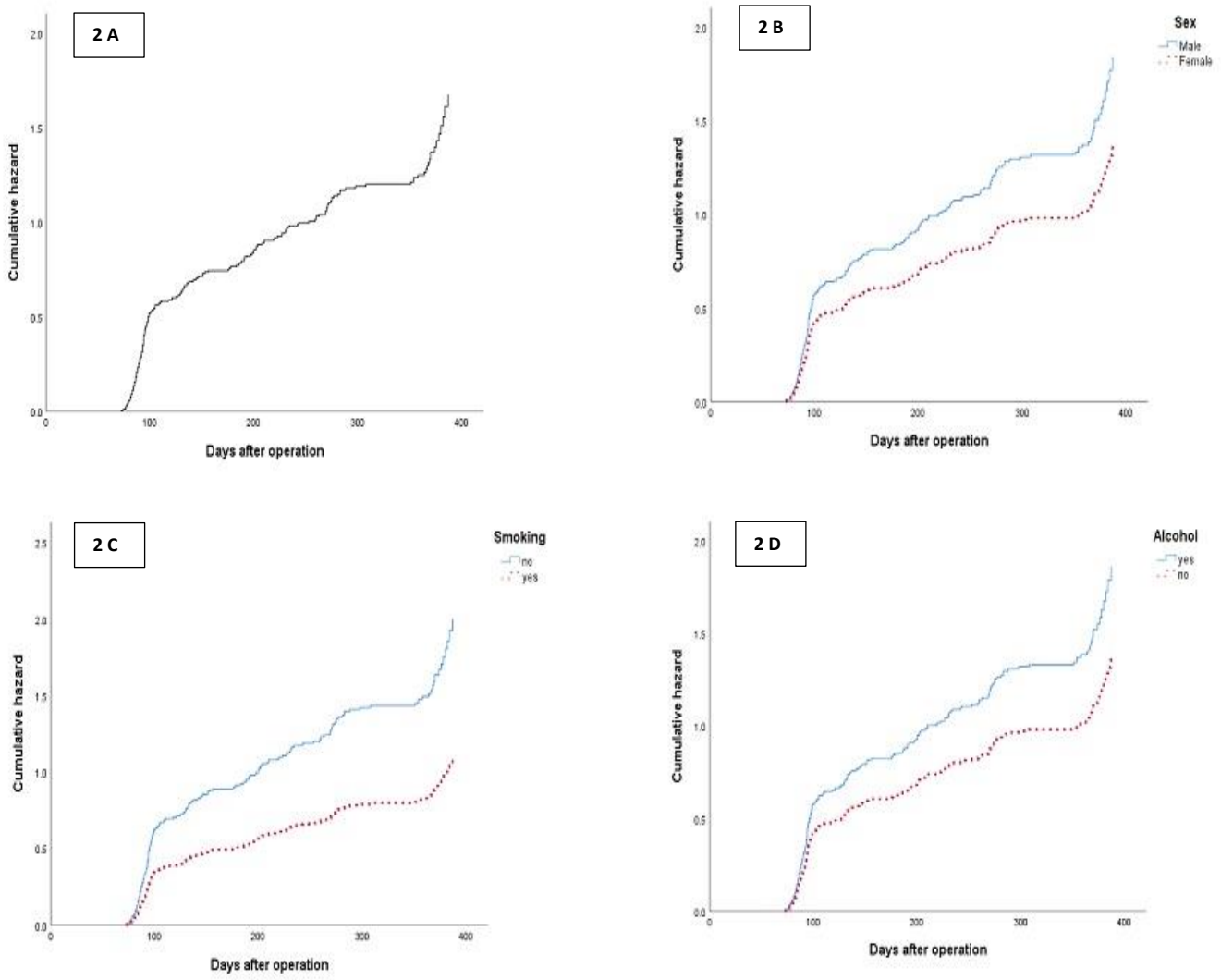

Figure 2A-D: Kaplan-Meier curves for resolution of troublesome post-operative pain amongst patients with tibial fracture: (A) overall results; (B) results by gender; (C) results by smoking status; (D) results by alcohol consumption status.

DISCUSSION

We found that 65.1% of patients who underwent repair of closed or open tibial shaft fracture achieved stable resolution of troublesome pain 3 to 12 months after surgery; the remaining 34.9% continued to report persistent troublesome pain. Few patients achieved resolution prior to 26 weeks; of those followed for 36 weeks or more almost three quarters of patients achieved resolution (Table 2, Figure 1). Independent predictors of resolution of troublesome pain were male sex, non-smoking and drinking alcohol (Table 3, Figure 2). The association was particularly strong for smoking status: non-smokers were almost twice likely to be free of pain than were smokers (HR=1.74, 95% CI, 1.33 to 2.29). We did not find significant association between age, obesity, additional injuries, post-operative weight-bearing status on the day of surgery and, perhaps most surprisingly, type of fracture (open versus closed) and persistent troublesome pain.

Strengths of this study include multicenter participation from two countries, which enhanced generalizability, a sample size sufficient to generate satisfactory confidence intervals, a follow-up period of one-year achieved in the majority of patients, a patient-important and conservative outcome definition of resolution of troublesome pain, [12,13] and analytic approaches.

However, this study also has limitations. First, the study failed to obtain 100% follow-up for all enrolled patients. We applied a time-to-event analysis (Cox regression) and provided results of complete observed data, which provides some assurances that loss to follow-up was unlikely to bias our results. Second, according to design of the TRUST, we were only able to measure our event, resolution of pain, at time of patient visits (6, 12, 18, 26, 32, 38, 44 and 52 weeks after surgery), rather than the actual time point of the troublesome pain resolution. Finally, data regarding a number of other potential predictors that other investigators have addressed was not available in our cohort. In particular, we did not explore the role of level of education [21-25], pre- or post-injury depression, anxiety and/or distress [21,23,24,26-28], acute post-surgical pain [21,23-25], pre-surgical physical dysfunction [23-25], somatic pre-occupation or impaired coping [29-32], receipt of disability benefits/involvement in litigation [33], or use of opioids [27,34,35], which may be relevant in terms of prognostic implications.

PPSP is common among patients with orthopedic injuries. Rivara and colleagues reported that in 527 patients with lower extremity fractures, 63.9% reported some pain at one year after injury with a mean (SD) severity of pain of 5.6 (4.9) on a 0 (none) to 10 (worst possible pain) point scale [24]. Castillo and colleagues reported that 33.3% had moderate or severe pain intensity among patients with tibia fractures at 7 years after injury [27]. The proportion of persistent, troublesome post-operative pain in our study, approximately 35% for all follow-up and just over 25% for those followed six months or more, was substantially lower than the value reported by Rivara, though not substantially different than Castillo [24,27]. Rivara did not separate the results of patients with tibia fractures from the overall results, which included patients with any type of lower extremity fracture [24]. Also, Rivara only reported the

proportion of any pain [24] while Castilo reported proportions of no pain, low, moderate and severe pain separately [27]. These may explain the difference.

The association we found of female sex being at a higher risk of PPSP is consistent with the results of prior studies examining trauma patients [21,23,24,36]. A large, prospective observational study by Holbrook and colleagues indicated that women had not only worse pain, but also significantly worse short- and long-term functional and psychological outcomes after major trauma than men [37]. The mechanisms of gender differences observed in chronic pain are not yet clear. Hypothetical explanations may include generic [38], socio-psychological [37,39], and enhanced central sensitization in women after orthopedic trauma [40].

Our finding of the association between smoking and persistence of troublesome pain is also consistent with prior studies [21,23,24,41]. For instance, Rivara and colleagues found that pre-injury smokers had higher risk of pain presence and pain severity one year after trauma: mean (SD) scores of pain were 5.8 (4.9) for smokers and 5.2 (4.6) for non-smokers, respectively ($p<0.001$) [24].

With regard to alcohol assumption and PPSP, prior studies have reported inconsistent results [21,23]. Castillo and colleagues found high levels of average alcohol consumption at baseline predicted chronic pain 7 years after limb threatening lower extremity trauma [27]. In a study by Rivara and colleagues, self-reported hazardous alcohol drinkers had lower pain severity, but did not differ in pain presence compared to the other two groups of nonhazardous drinkers or non-drinkers one year after trauma [24]. Thus, our finding of alcohol consumption being associated with a lower risk of persistent troublesome pain is consistent with the reports by Walker-Bone and Rivara [24,36] but not with the report by Castillo [27]. The data in our study did not allow us to distinguish between hazardous and nonhazardous drinkers.

We did not find obesity and severity of injury to be predictors of persistent troublesome pain. Our results are consistent with a Dutch cohort study of trauma patients in terms of BMI [22] and a systematic review of orthopedic trauma patients in terms of injury severity [21]. Prior evidence also indicated that older age is associated with persistent pain after trauma surgery [21,23]; however, age was not associated with persistent troublesome pain in our cohort.

CONCLUSION

Our findings suggest that clinicians should be particularly alert to the possibility of troublesome post-operative pain in female smokers who do not drink alcohol. Clinicians may consider counseling patients to discontinue smoking, inform them that they are at nearly double the risk of incidence of troublesome post-operative pain (in addition to the long-term adverse health consequences of smoking). Our findings regarding associations of troublesome post-operative pain with female sex and smoking appear robust: they are consistent with a number of prior reports. Subsequent prospective studies addressing issues of age and alcohol consumption would likely add further valuable evidence. Such studies would ideally have a sufficient sample size, follow-up duration, completeness of follow-up, and collect data on all possible predictors of PPSP.

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Conflicts of interest

No conflicts declared.

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	The TRUST Investigators (details in Appendix 1)	The TRUST Investigators recruited all the patients in TRUST, and performed the primary data collection and data cleaning. The TRUST Investigators released the data for current study.

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