Factors Associated with Recurrence in Chronic Subdural Hematoma following Surgery

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Abstract

Background Recurrence is a frequent complication after surgery in a chronic subdural hematoma (CSDH). This study aimed to describe the recurrent rate of CSDH after surgery. In addition, a secondary objective aimed to explore factors associated with the recurrence of CSDH after surgery.

Methods A total of 141 surgical CSDH patients were analyzed in this retrospective study. The Cox regression method was used to conduct both univariate and multivariate analyses of variables associated with recurrence. As a result, the cumulative incidence of recurrence for each covariate survival curve was built after the final model.

Results Twenty-two percent of the patients showed evidence of recurrence. Initially, four variables (Glasgow coma scale score 3–8, clopidogrel, operative time, and amount of irrigated saline) had potential factors in univariate analysis but only clopidogrel and amount of saline irrigation were significantly associated with CSDH recurrence.

Conclusion Preoperative clopidogrel and the amount of saline irrigation were found to be associated with the recurrence rate. Factors associated with CSDH recurrence should be developed and validated as the clinical prediction tool for implication in general practice.

Keywords
- Chronic Subdural Hematoma
- burr hole
- recurrence
- traumatic brain injury

Introduction

Chronic subdural hematoma (CSDH) is a frequent condition among the elderly. From a population-based study, the incidence of CSDH was reported between 8.2 and 17.6 per 100,000 persons per year.[1] The prevalence of CSDH is currently rising due to an aging population and the increased use of antiplatelet and anticoagulant medicines.[2] The treatment of choice for symptomatic patients is surgery, including craniotomies, twist drills, and burr holes.[3,4] However, recurrence rates following surgery have been observed to range from 10.1 to 29% in prior studies.[5–8]

In recent years, several risk factors for the recurrence of CSDH have been identified as follows age, seizure, coagulopathy, type of CSDH, the thickness of the hematoma, postoperative midline shift, postoperative subdural air collection, and postoperative re-expansion.[9–13] However, risk factors for recurrence are still the subject of controversy, and there is no universal consensus. Moreover, previous studies analyzed the factor as a binary outcome with various time points for recurrence that have been inconsistent. Time-to-event analysis has been used to investigate factors that may have an impact on the outcomes during follow-up, especially neuro-oncology.[14,15]

Therefore, the purpose of this study was to describe the recurrent rate of CSDH after surgery. Additionally, a secondary objective was to evaluate factors associated with the recurrence of CSDH after surgery by time-to-event analysis.

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Materials and Methods

Study Design and Study Population

A retrospective study was conducted on all CSDH patients who underwent surgery between 2009 and 2021. However, we eliminated patients with bilateral CSDH, inaccessible preoperative cranial computed tomography (CT), inaccessible postoperative cranial CT, and inaccessible medical records.

The clinical characteristics and imaging findings of patients were collected with a structured record form, including age, gender, cause of CSDH, Glasgow coma scale (GCS) scores, signs, symptoms, underlying disease, and preoperative medication. Preoperative GCS was categorized as follows; mild traumatic brain injury (TBI; GCS scores 13–15), moderate TBI (GCS scores 9–12), and severe TBI (GCS score 3–8).[16] Preoperative and postoperative neuroimagings were reviewed for several characteristics of CSDH by two neurosurgeons. The CSDH classification was categorized according to Nakaguchi et al.[17]

In addition, the detail of the treatment was reviewed as follows: type of operation, drain placement, number of burr hole, operative time, and drain placement. Moreover, all burr hole operations in our institute were performed with saline irrigation; therefore, the amount of saline in each case was recorded in an electronic database. Operative time was defined as the time of incision to complete wound closure and the amount of saline irrigation was collected from an operative note in an electronic medical record database. Moreover, the percent of re-expansion of the cortex after surgery was estimated according to Mori et al.[13]

Recurrence was defined as an increase in the CSDH thickness on the side that had undergone surgery when compared with the results of the first postoperative CT scans or the patient developed neurological deterioration during follow-up. Postoperative cranial CT scans were used to examine the recurrent event at each subsequent visit until July 31, 2022, which served as the final date.

A human research ethics committee approved this study (REC 64–395–10–1, September 14, 2021). This study did not require informed consent from patients because the study design was a retrospective approach. Additionally, the patient's identification numbers were encoded before analysis.

Statistical Analysis

Descriptive statistics, which were presented as percentages for categorical data and mean + standard deviation (SD) for continuous variables, were used to determine clinical features and imaging findings. The prognosis of both the recurrent group and nonrecurrent group was evaluated as a time-to-event analysis using the cumulative Kaplan–Meier curve and the log-rank test. Using Cox regression analysis, the factors associated with recurrence were presented as a hazard ratio (HR) with 95% confidence interval (CI). Therefore, a multivariable model with backward stepwise selection was used to investigate the candidate variables that had a *p*-value of 0.1 or less in the univariate analysis. The *p*-values less than 0.05 were observed as statistically significant, and the Akaike information criterion (AIC) with clinical relevance was used for model selection. In addition, the HR of continuous variables significantly associated with recurrence was plotted to evaluate the cutoff point for the protective effect of the recurrent event of CSDH.[18,19] The statistical analysis was done using the R version 4.4.0 software (R Foundation, Vienna, Austria).

Results

Clinical Characteristics and Imaging Findings

The study population before analysis was 141 and baseline characteristics are listed in ►**Table 1**. The mean age of the patients was 65.56 years (SD: 17.16); therefore, patients 65 years or older were found in 64.5% of the present cohort. The majority (80.1%) of them were male and 23.4% were the unknown cause of CSDH. Preoperative aspirin usage was found in 20.6%, while 6.4% of the present cohort had clopidogrel usage before the operation. Moreover, preoperative warfarin usage was observed in 7.1% of cases. Before surgery, almost of patients had GCS 13 to 15 (86.5%), GCS 9 to 12 (5.7%), and GCS 3 to 8 (7.8%).

Preoperative cranial CT findings are revealed in ►**Table 2**. Half of CSDH patients were homogenous type, while the separated type was found in 21.9%. Almost CSDH was placed in the frontoparietal convexity. In addition, the mean thickness of CSDH before surgery was 20.43 mm (SD: 7.29), whereas the mean preoperative midline shift of CSDH was 8.69 mm (SD 5.16). More than two-thirds had obliterated basal cisterns in this study.

Treatment and outcome following surgery are shown in ►**Table 3**. The majority of operation was burr hole with irrigation in 92.2%, while craniotomy was performed in 7.8% of all cases. The mean operative time was 92.42 minutes (SD: 47.63) and the mean percent of brain re-expansion was 43.92% (SD: 24.16) Furthermore, 81.5% of cases were found in postoperative intracranial air. During follow-up, the mean follow-up time was 130.74 days (SD: 58.36) and the recurrent rate was observed in 22% of total cases. Mortality did not occur in this study during follow-up.

Factors Associated with Recurrence of CSDH following Operation

The univariate analysis was performed on various clinical variables using Cox hazard regression. Initially, the significant factors included preoperative clopidogrel usage (HR: 4.00, 95% CI: 1.53–10.46), preoperative GCS scores (GCS: 13–15 = reference, HR of GCS 3–8: 4.25, 95% CI: 1.71–10.54), operative time (HR: 0.97, 95% CI: 0.95–0.98), and amount of saline irrigation (HR: 0.99, 95% CI: 0.991–0.999), respectively.

Therefore, a backward stepwise selection method was performed to evaluate the potential variables associated with the recurrence of CSDH. As shown in ►**Table 4**, the model with the lowest AIC included preoperative clopidogrel usage (HR: 3.26, 95% CI: 1.21–8.76), operative time (HR: 0.98, 95% CI: 0.96–0.99), and amount of saline irrigation (HR: 0.99, 95% CI: 0.992–0.998), respectively.

Table 1 Demographic data of patients with chronic subdural hematoma ($n = 141$)

Characteristics	*n* (%)
Gender	
Male	113 (80.1)
Female	28 (19.9)
Mean age—year (SD, standard deviation)	65.56 (17.16)
Comorbidity	
Hypertension	52 (36.9)
Dyslipidemia	30 (21.3)
Diabetes mellitus	25 (17.7)
Cerebrovascular disease	13 (9.2)
Liver disease (hepatitis or cirrhosis)	5 (3.5)
Renal failure	9 (6.4)
Antiplatelet/anticoagulant usage	
Aspirin	29 (20.6)
Clopidogrel	9 (6.4)
Warfarin	10 (7.1)
Enoxaparin	2 (1.4)
Cause	
History of traumatic brain injury	103 (73.0)
Over drainage from shunt	5 (3.5)
Unknown cause	33 (23.4)
Signs and symptoms	
Progressive headache	
Weakness	74 (52.5)
Alteration of consciousness	39 (27.7)
Ataxia	70 (49.6)
Seizure	3 (2.1)
Preoperative Glasgow coma scale score	
13–15	122 (86.5)
9–12	8 (5.7)
3–8	11 (7.8)
Pupillary light reflex	
React both eyes	139 (98.6)
Fixed one eye	1 (0.7)
Fixed both eyes	1 (0.7)
American Society of Anesthesiologists (ASA) class	
2	1 (0.7)
3	2 (1.4)
4	2 (1.4)
5	136 (96.5)

Table 2 Preoperative imaging, treatment, and outcome of patients with chronic subdural hematoma ($n = 141$)

Factor	*n* (%)
Preoperative imaging	
Type of CSDH	
Homogenous	72 (51.0)
Hyperintensity	5 (3.5)
Isointensity	20 (14.2)
Hypointensity	47 (33.3)
Trabecular	13 (9.2)
Laminar	25 (17.7)
Separated	31 (21.9)
Separated subtype	20 (14.2)
Gradation subtype	11 (7.8)
Location	
Frontal convexity	2 (1.4)
Frontoparietal convexity	137 (97.2)
Frontal base	2 (1.4)
Frontotemporal base	0
Mean thickness of CSDH—mm (SD)	20.43 (7.29)
Thickness of CSDH—mm	
< 20	68 (48.2)
≥ 20	73 (51.8)
Mean midline shift of CSDH—mm (SD)	8.69 (5.16)
Midline shift-mm	
< 5	27 (19.1)
≥ 5	114 (80.9)
Preoperative basal cistern	
Patent	45 (31.9)
Obliteration	96 (68.1)

Abbreviations: CSDH, chronic subdural hematoma; SD, standard deviation.

Cutoff Points of the Continuous Covariates for Protective Effect to Recurrence

Following that, the effect of the significant continuous covariates (operative time and amount of saline irrigation) was estimated by the hazard plots, as shown in ►**Fig. 1**. As a result, the cutoff points of these covariates that led to the HR of less than 0 for the protective effect of recurrence were 90 minutes for operative time and 3,200 mL for the amount of saline irrigation. For simplifying the final model, operative time and amount of saline irrigation were categorized into binary classifiers as their cutoff points. Therefore, the cumulative Kaplan–Meier curves was shown in ►**Fig. 2A–D**. Finally, the effect of the predictors related to the recurrent event and the final model that comprised the categorical variables were shown in ►**Fig. 3A–D**.

Table 3 Treatment and outcome following surgery ($n = 141$)

Factor	*n* (%)
1st operation	
Burr hole with irrigation	130 (92.2)
Craniotomy	11 (7.8)
Mean operative time—min (SD)	92.42 (47.63)
Mean amount of saline irrigation—mL (SD)	3300.70 (2106.13)
Drain placement in 1st operation	
No	52 (36.9)
Subgaleal drain	87 (61.7)
Subdural drain	2 (1.4)
Number of burr hole ($n = 130$)	
Single burr hole	51 (39.2)
Two burr holes	79 (60.8)
Postoperative imaging (2nd CT)	
Mean percent of brain re-expansion-%	43.92 (24.16)
Percent of brain re-expansion	
< 50%	77 (54.6)
≥50%	64 (45.4)
Intracranial air	
No	26 (18.4)
Minimal	36 (25.5)
Obvious	79 (56.0)
Outcome	
Mean follow-up time—day (SD)	130.74 (158.36)
Recurrence rate	31 (22.0)

Abbreviations: CT, computed tomographic; SD, standard deviation.

Discussion

The natural courses of CSDH following surgery were either resolved or recurrent. The recurrent rate of CSDH was found at 22% in this study. From prior studies, Oh et al[6] investigated the postoperative course of CSDH and reported that 12% of patients had recurrent CSDH, while Schwarz et al[7] observed a recurrent rate of CSDH after burr hole operation in 29%. In addition, recurrence rates following surgery have been reported from other prior studies to range from 8.9 to 29.1%.[20,21]

Because various criteria for the recurrence were used, there are different recurrent rates from each other. Moreover, several time endpoints for recurring criteria varied between 3 and 6 months.[17,22] Therefore, we proposed to use time-to-event statistical analysis to evaluate the postoperative course of CSDH that is a challenge because previous studies estimated outcomes by binary logistic regression that had various time endpoints and led to various results. When there are several time endpoints, a time-to-event analysis may better capture the natural course of CSDH and be more appropriate than binary logistic regression.[14,15]

Risk factors related to the recurrence of CSDH following surgery have still been discussed and are uncertain from prior studies. As result, preoperative clopidogrel usage and the amount of saline irrigation were potentially associated with the recurrence of CSDH in this study.

The use of antithrombotic drugs, either antiplatelets or anticoagulants, has increased due to the patient's underlying disease.[23,24] Around 35% of patients with CSDH in this study had preoperative antithrombotic drug usage and we found clopidogrel was significantly associated with recurrence. These drugs have been debated as a risk factor for recurrence from prior studies. Leroy et al[23] reported that preoperative anticoagulant usage was the predictor of CSDH recurrence, while other prior studies found that antithrombotic therapy did not affect the recurrent event.[10,13,24] Discontinuation of antithrombotic drugs was performed before surgery, but there are variations in the recommencing time of antithrombotic drugs in the postoperative period.[25] Early recommence of antithrombotic drugs may lead to a recurrence of CSDH. However, the optimal time of restart should be further studied in the future. Moreover, aspirin, which is another antiplatelet, was not associated with the recurrence of CSDH in this study that is explained by the different mechanisms of action between aspirin and clopidogrel. Aspirin irreversibly inhibits platelet cyclooxygenase-1,[26] while clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation.[27] However, more research about the impact of various antiplatelet or anticoagulant medications has to be conducted in the future.

Intraoperative saline irrigation has been reported to significantly reduce CSDH recurrence compared with no irrigation in prior studies.[28–30] Moreover, the amount of saline irrigation has noteworthy importance for reducing recurrent rates when at least 3,200 mL of saline was used by the HR plot. Initially, we analyzed this variable as a continuous variable and found that the amount of saline irrigation significantly affected a reduction of risk of recurrence (HR: 0.99, 95% CI: 0.992–0.998 in multivariable analysis). However, the continuous variable was dichotomized to make it easier to use in general practice and the HR plot is the one of cutoff optimization methods that have been used.[31,32] As a result, the amount of saline irrigation was dichotomized at 3,200 mL of saline and it was discovered that HR was less than zero and had a protective effect against the recurrence of CSDH.

Irrigation washes out several inflammatory cytokines and fibrinolytic factors; this procedure may help reduce postoperative recurrence.[30] In addition, operative time was related to a low recurrent rate in univariate analysis, but this factor did not significantly associate with CSDH recurrence. From multivariable analysis, operative time had influent less than other factors. To the author's knowledge, this is the first study to report that amount of saline irrigation is significantly related to the recurrence of CSDH following surgery. The

Table 4 Factors associated with recurrence after surgery using Cox hazard regression analysis

Factor	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Sex				
Male	Ref			
Female	0.94 (0.36–2.46)	0.90		
Age group—year				
< 60	Ref			
≥60	0.54 (0.26–1.15)	0.11		
Underlying disease				
DM[a]	1.07 (0.43–2.62)	0.88		
Hypertension[a]	0.39–1.78	0.64		
Lipidemia[a]	1.08 (0.46–2.53)	0.84		
Liver disease[a]	3.20 (0.75–13.63)	0.11		
Renal failure[a]	0.04 (0.01–27.82)	0.34		
Preoperative medication				
Aspirin[a]	1.25 (0.53–2.91)	0.60		
Clopidogrel[a]	4.00 (1.53–10.46)	0.005[a]	3.26 (1.21–8.76)	0.02
Warfarin[a]	1.37 (0.41–4.54)	0.59		
Enoxaparin[a]	0.04 (0.01–172.55)	0.64		
Signs and symptoms				
Alteration of consciousness[a]	1.35 (0.63–2.89)	0.43		
Weakness[a]	0.87 (0.42–1.80)	0.72		
Ataxia[a]	0.65 (0.22–1.88)	0.43		
Headache[a]	0.87 (0.42–1.78)	0.70		
GCS score				
13–15	Ref			
9–12	1.65 (0.38–7.05)	0.49		
3–8	4.25 (1.71–10.54)	0.002[a]		
Pupillary light reflex				
React both eyes	Ref			
Fixed one eye	0.99 (0.01–405.7)	1.00		
Fixed both eyes	20.47 (0.02–217.1)	0.71		
Type of CSDH				
Homogenous	Ref			
Separate and gradation	0.60 (0.22–1.64)	0.32		
Trabecular	0.62 (0.14–2.68)	0.52		
Laminar	1.04 (0.41–2.66)	0.92		
Thickness of CSDH—cm				
< 2	Ref			
≥2	0.59 (0.28–1.24)	0.17		
Preoperative midline shift—mm				
< 5	Ref			
≥5	0.77 (0.33–1.80)	0.55		

(*Continued*)

Table 4 (*Continued*)

Factor	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Preoperative basal cistern				
Patent	Ref			
Obliteration	0.91 (0.42–1.95)	0.82		
Type of operation				
Craniotomy	Ref			
Burr hole	2.68 (0.36–19.71)	0.33		
Number of burr hole				
Single	Ref			
Two	0.94 (0.45–1.98)	0.88		
Postoperative drain placement				
No	Ref			
Yes	1.02 (0.48–2.16)	0.94		
Operative time—min (incision to close wound time)	0.97 (0.95–0.98)	0.001	0.98 (0.96–0.99)	0.01
Amount of saline irrigation—mL	0.99 (0.991–0.999)	0.001	0.99 (0.992–0.998)	0.01
Percent postoperative re-expansion				
< 50%	Ref			
≥50%	0.75 (0.36–1.55)	0.44		
Postoperative intracranial air				
No	Ref			
Yes	1.19 (0.45–3.12)	0.71		

Abbreviations: CSDH, chronic subdural hematoma; CI, confidential interval; DM, diabetes mellitus; GCS, Glasgow coma scale.
[a]Data show only “yes group” while reference groups (no group) are hidden.

findings of this study lend credence to the idea that inflammatory cytokines and fibrinolytic agents wash out to lower the recurrence rate.

Moreover, the use of postoperative drains has been studied and the results of this intervention still have been inconclusive for the predictor of recurrence. Weigel et al reviewed publications and reported that drainage reduces the risk of recurrence,[4] while studies by Gernsback et al and Nath and Fotedar found that recurrence rates of CSDH do not appear to be affected by either the number of burr holes or the number of drains.[33,34] According to the findings in this study, the use of a drain was not associated with the recurrence of CSDH, which is consistent with previous research.

There are certain limitations to the study that should be pointed out. This study was limited by its single-center design and retrospective nature, which may have led to bias. However, we tried to adjust the confounders by multivariable analysis.[35,36] In addition, another limitation was relatively small of cases overall. Thus, prospective or randomized controlled research is required for a larger sample size and a homogenous protocol to confirm the effect of predictors.

Conclusion

In summary, preoperative clopidogrel and saline irrigation were found to be associated with the recurrence rate of CSDH. Factors associated with CSDH recurrence should be developed and validated as the clinical prediction tool for implication in general practice.

Ethical Approval

A human research ethics committee of Faculty of Medicine, Prince of Songkla University approved this study (REC 64–395–10–1) on September, 14 2021.

Authors' Contributions

K.B. and T.T. conceived the study and designed the method. K.B. supervised the completion of the data collection. T.T. undertook the recruitment of participating centers and patients and managed the data, including quality control. T.T. provided statistical advice on the study design and analyzed the data, while K.B. drafted the manuscript, and all authors contributed substantially to its revision. T.T. and K.B. take responsibility for the paper as a whole.

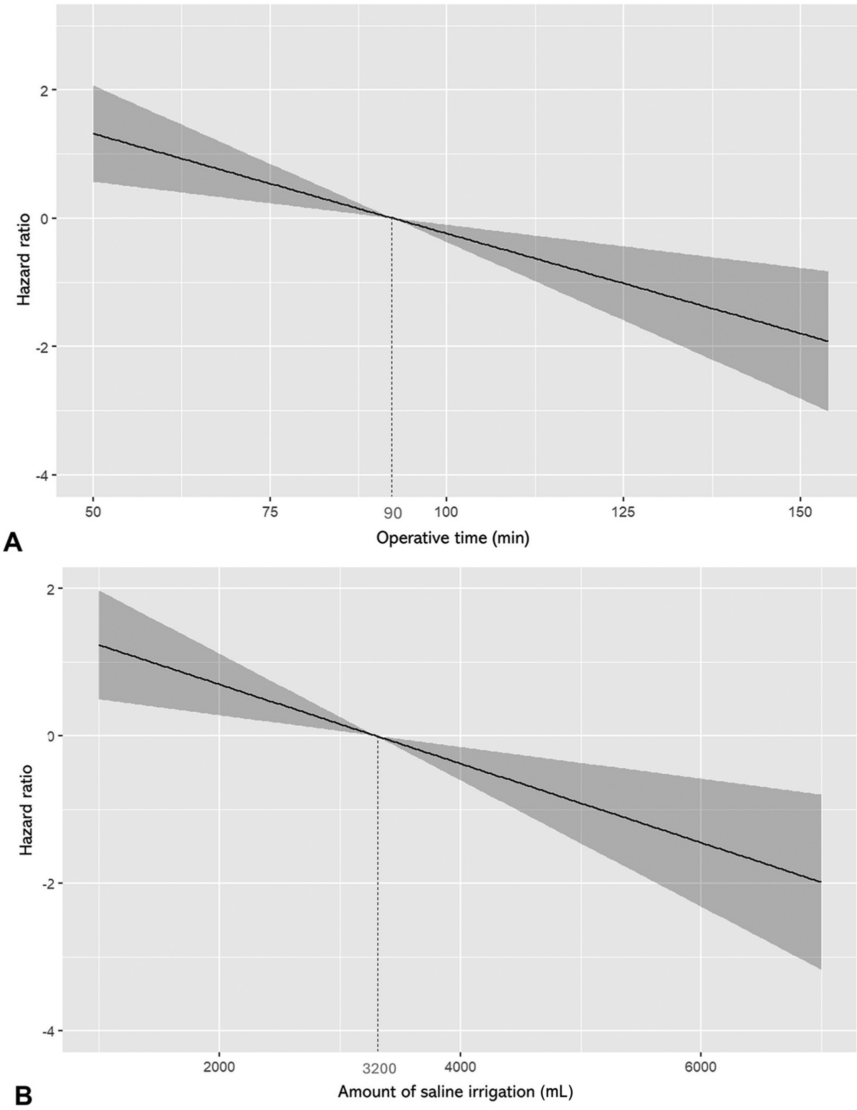

Fig. 1 Hazard plot of continuous variables for recurrence of chronic subdural hematoma. (**A**) Operative time. (**B**) Amount of saline irrigation.

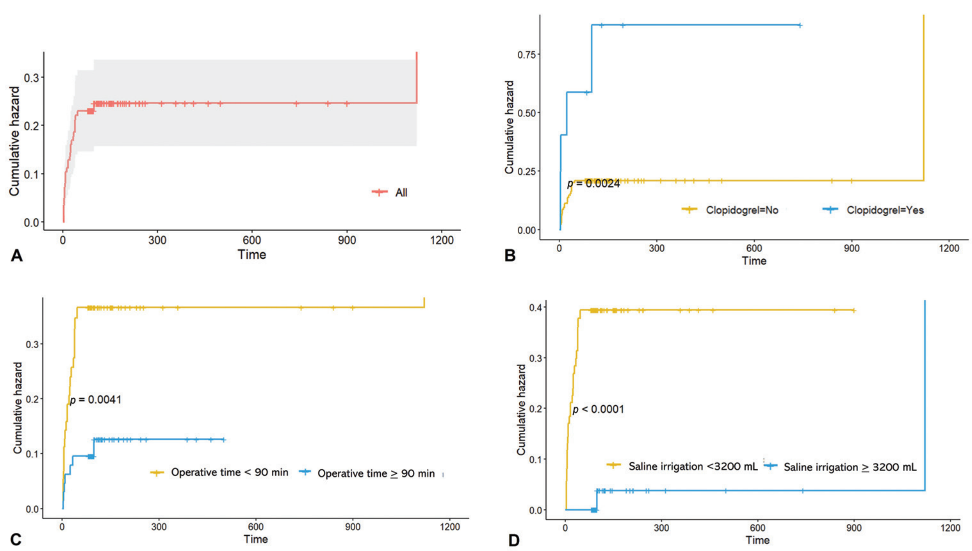

Fig. 2 Cumulative Kaplan–Meier curves for recurrence after surgery. (**A**) Overall cumulative Kaplan–Meier curves. (**B**) Clopidogrel, (**C**) Operative time. (**D**) Amount of saline irrigation.

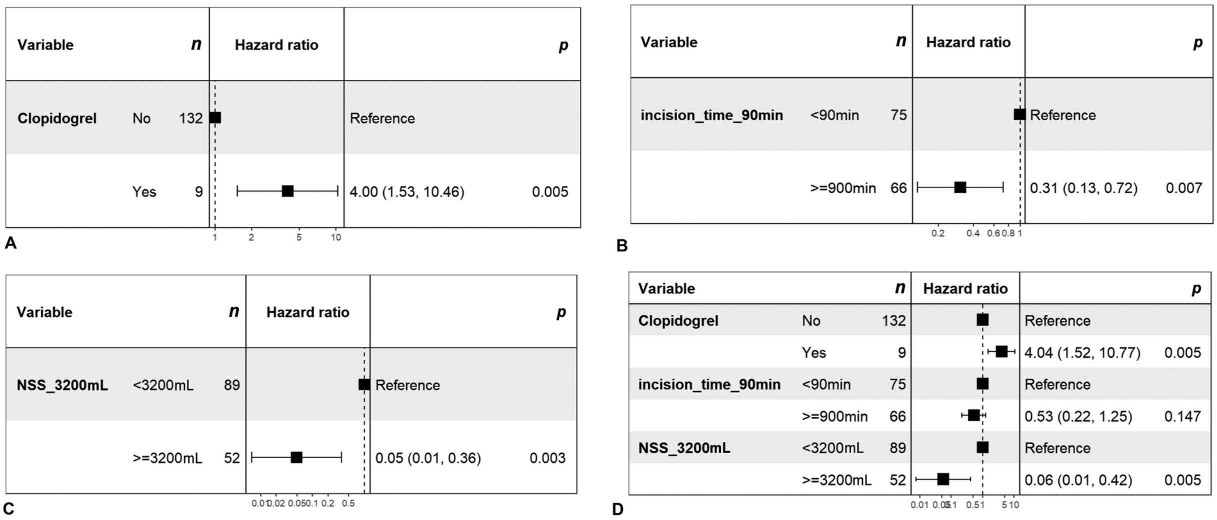

Fig. 3 Forest plots of the hazard ratio of each covariate. (**A**) Clopidogrel with univariate analysis. (**B**) Operative time (incision-closure wound time) with univariate analysis. (**C**) Amount of saline irrigation with univariate analysis. (**D**) Multivariable model.

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Conflict of Interest
None declared.

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