The impact of asprin use on the outcome of patients admitted to the intensive care unit with COVID-19 infection

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Abstract

Background

Our objective in this study is to know the impact of the use of asprin in anti-aggregation dose on the evolution during hospitalization of patients admitted in intensive care unit for a severe infection by SARS-COV-2.

Methods

We conducted a prospective study of patients admitted to our department with severe COVID-19 infection during the period between March 2020 and March 2022, analyzing the difference between the placebo group and the aspirin group on the primary endpoint of all-cause hospital mortality and the composite secondary endpoint of use of mechanical ventilation and thromboembolic events.

Results

Out of 1124 patients included, 32.6% died, with a protective effect of aspirin against placebo (Hazard-ratio = 0.691, p = 0.003), for thrombo-embolic complications, 104 events were observed, with a protective effect of aspirin (Hazard-Ratio = 0.448 and p = 0.001), finally regarding mechanical ventilation, there was no remarkable benefit on our sample.

Conclusion

Given the divergence of results of studies published in the literature, the availability of results of large randomized controlled trials is a necessity.

Introduction

It is currently demonstrated that COVID-19 disease is a disease with a very important thrombogenic power [1], therefore a clear physio-patological understanding of the concept of thrombosis during COVID-19 infection could open a new therapeutic approach to reduce the morbidity and mortality of this disease [2]. In a very simple way, the thrombogenic potential of SARS-COV-2 can be explained by the following phenomena: hyperinflammation [3], platelet activation [4], endothelial dysfunction [5], and finally coagyulopathy [6]. From these pathophysiological hypotheses, we can deduce that the use of low-dose aspirin could have a beneficial effect in patients with COVID-19 infection, due to its anti-inflammatory, anti-platelet activation, anti-coagulant and pleotoric effect on endothelial function [7], adding to this, the anti-viral effect of aspirin demonstrated against RNA viruses in the respiratory tract [8]. For all these reasons, the use of low-dose aspirin in hospital or not could have a beneficial effect on the short- and long-term evolution of these patients.

Based on this reasoning, we have carried out a prospective study in order to deduce the effect of aspirin on the intra-hospital and one year evolution of patients hospitalized for a severe form of covid-19 disease.

Materiels Et Methodes

Type, aims of the study and Study Participations

At the beginning of the pandemic, several physiopathological hypotheses defended the thrombogenic power of the COVID-19 virus, for this reason, we had the idea to know the effect of aspirin in patients admitted in ICU for a severe form of the disease on the evolution of these patients.

Our objective is to determine the benefit of the daily use of aspirin at anti-aggregation dose (75mg/day orally) in our patients on intra-hospital mortality from all causes as a primary outcome and as a composite secondary outcome of thrombo-embolic complications of all types (pulmonary embolism, (pulmonary embolism, myocardial infarction, acute limb ischemia, deep vein thrombosis, ischemic stroke) as well as the use of mechanical ventilation in patients hospitalized for serum COVID-19 infection. For this purpose, we conducted a prospective study on patients admitted in intensive care unit of the CHU Mohammed VI of OUJDA, over a period between March 2020 (which is the beginning of inclusion of patients) and March 2022 (the end of inclusion). All patients included in study had a thoracic imaging, an arterial gasometry and a biological check-up at admission, followed by a multi-daily monitoring of the clinical condition, and thus the possible complications mainly thrombo-embolic events. the follow-up of patients interested in the length of hospitalization.

We included 1122 patients, randomly divided into two groups and this after having the ethical approval of the patients for the participation in the study on the one hand, and the agreement to prescribe the treatment in the Aspirin group on the other hand:

Group 1: patients who received a placebo with the national anti-COVID-19 protocol dedicated to ICU patients composed of: (Azithromocyin 500mg then 250mg for 4 days, Vitamin C 1000mg/12hours, Zinc 45mg/day, Enoxaparin 6000UI/12hours and Corticosteroid therapy).

Group 2: patients who received in addition to the national anti-COVID-19 protocol, Aspirin 75mg/day orally for the duration of the hospitalization.

Data Collection

Medical information was collected prospectively by the medical staff of the unit and stored in the medical observation database used at CHU MOHAMMED VI OUJDA. For each patient, the collection took into account demographic information (sex, age). The medical and surgical history, anamnestic data concerning the infection including the duration of symptoms, the duration between the beginning of symptoms and the consultation, the symptoms of the COVID-19 infection, biological and imaging data,

the treatment used during the hospitalization, then the evolution with regard to the complications presented and mortality.

Statistical analysis

The objective of the study was to determine the benefit of aspirin on mortality as a primary outcome, and a composite outcome of thromboembolic complications and the use of mechanical ventilation in patients hospitalized in our intensive care unit for severe COVID-19 infection.

For this purpose, our population was divided into two groups: the group of patients who received asiprin and the group of patients who received placebo. Data were collected and processed on IBM SPSS statistics 26.0 statistical software. Normally distributed quantitative variables were described as mean and standard deviation, and analyzed between the two groups by the t-student test. Quantitative variables not normally distributed were described as median and interquartile range, and analyzed by nonparametric tests (U-mann whitney test). The qualitative variables were described in numbers, and the analysis between the two groups was done by Pearson's chi-square test or Fisher's exact test. Anonymity and confidentiality were respected in all stages of data processing.

For the primary outcome, a Cox proportional hazards regression analysis adjusted for the main variables described in the literature as a risk factor for mortality (age, previous heart disease, D-dimer level, and mechanical ventilation) was performed with the associated 95% confidence interval (CI) and two-sided p-value reported and a p-value less than 0.05 was considered statistically significant. For secondary outcomes, a logistic regression statistical analysis was applied. First, a univariate approach was performed for all covariates, and then a multivariate analysis was performed for all covariates that had a statistically significant result in the univariate analysis with an associated 95% confidence interval (CI) and two-sided p value were reported. For all statistical tests, a p value less than 0.05 was considered statistically significant.

Ethical aproval

This study was approved by the Mohammed Ith University ethical committee for biomedical research in OUJDA (Morocco) under the number 017/20.Access to patient data was authorized by the Mohammed VI university hospital and approved by the head of the department, and this after having the signed consent of the patients for participation in the study. For both groups, an informed consent was presented to each patient upon admission, for the explanation of the interest of the study, and the potential benefit expected as well as the complications on the use of aspirin. All included patients granted their participation in the study, with a signed consent. Data anonymity was respected in accordance with national and international guidelines.

Results

1) Characteristics of the Patients

Of the 1124 patients included in our study, 63.6% were men, mean age of the patients was 64 with a significant difference between the aspirin and placebo groups. For the duration of hospitalization, there was no significant difference between the two groups, with a median of 6 for the placebo group and 10 for the aspirin group. The most frequent comorbidity was diabetes with 32% in our population, followed by arterial hypertension 31.5%, heart disease 15% and finally obesity by 15.7%. For all comorbidities, there was no significant difference in median between the two groups. For clinical symptoms, fever and dyspnea were the most frequent symptoms with a consecutive rate of 79.2% and 78.6%.

On the biological level, the median of ferrtin in our patients was 1002.62 (IQR = 1536.08) without significant difference, the median of D-Dimer at 1.46 (IQR = 4.81) also without difference between the two groups, on the other hand, we observed a significant difference for the median of LDH, of the prothrombin level, and finally the median of procalcitonin. For blood gas analysis, there was a significant difference in median PCO2 with a median of 33.35 mmhg for the placebo group and 35 mmhg for the Aspirin group ($p = 0.0001$). For thoracic imaging, more than 65% of our patients had an estimated parenchymal involvement of more than 50% with a significant difference between the two groups.

For the therapeutic management, the most used corticosteroid therapy was methylprednisolone with 52% of our patients with a significant difference between the two groups, with a higher percentage in the aspirin group (64.3%), tociluzimab is used in 17. 1% of the patients, of which 70.7% in the aspirin group, the use of non-invasive ventilation is observed in 23.6% of the patients, with a higher percentage in the placebo group (33.5%) and a very significant difference compared to the aspirin group (18.4%). (Table 1 summarizes the comparative results between the two groups with respect to demographic, clinical, paraclinical and therapeutic characteristics)

Table 1
comparative results between the two groups with respect to demographic, clinical, paraclinical and therapeutic characteristics

	Whole population (N = 1124)	**Placebo (N = 412) Groupe A**	**Aspirin use (N = 712) Groupe B**	**pValue**
Age	64 (IQR = 16)	59.87 (IQR = 15)	64.97 (IQR = 23)	< 0,001
Sexe (%)	709 (63.6%)	285 (23.8%)	444 (39.9%)	0,170
• Male	405 (36.4%)	139 (12.5%)	266 (23.9%)	
• Female				
BMI	26 (IQR = 4.3)	26.40 (IQR = 5.13)	26.61 (IQR = 4)	0.594
Length of hospitalization	8 (IQR = 10)	8.03 (IQR = 8)	7.86 (IQR = 10)	0.853
Comorbidities	356 (32%)	129 (11.6%)	227 (20.4%)	0.522
Diabete (%)	351 (31.5%)	121 (10.9%)	230 (20.6%)	0.219
Arterial hypertension (%)	167 (15%)	59 (5.3%)	108 (9.7%)	0.428
Heart disease	175 (15.7%)	70 (6.3%)	105 (9.4%)	0.151
Obesity (%)	78 (7%)	27 (2.4%)	51 (4.6%)	0.428
Smoking (%)	33 (3%)	18 (1.6%)	15 (1.3%)	0.023
Asthma (%)	17 (1.5%)	3 (0.3%)	14 (1.3%)	0.083
COPD (%)	40 (3.6%)	17 (1.5%)	23 (2.1%)	0.250
STROKE (%)	60 (5.4%)	22 (2%)	38 (3.4%)	0.524
CKD (%)				
Clinical characteristics (%)	882 (79.2%)	307 (27.6%)	575 (51.6%)	0.029
Fever	876 (78.6%)	289 (25.9%)	587 (52.7%)	< 0,001
Dyspnea	741 (66.5%)	257 (23.1%)	484 (43.4%)	0.069
Asthenia	552 (49.6%)	173 (15.5%)	379 (34%)	< 0,001
headache				

	Whole population (N = 1124)	Placebo (N = 412) Groupe A	Aspirin use (N = 712) Groupe B	pValue
Biological findings (%)				
Ferritin (ug/L)	1002.62 (IQR = 1536.08)	937 (IQR = 1447.12)	1135 (IQR = 1768.48)	0.306
D-Dimere (mg/l)	1.46 (IQR = 4.81)	1.49 (IQR = 5.35)	1.39 (IQR = 3.68)	0.044
Fibrinogene (g/l)	6.5 (IQR = 3)	6.5 (IQR = 3.2)	6.5 (IQR = 2.6)	0.531
LDH (UI/l)	620 (IQR = 362.75)	620 (IQR = 330.25)	609 (IQR = 393.5)	0.004
Troponine US (ng/ml)	23.5 (IQR = 92.18)	27.95 (IQR = 132.7)	19.1 (IQR = 59.9)	0.4
TP (%)	72.5 (IQR = 19.25)	72.5 (IQR = 19.25)	72 (IQR = 20.75)	< 0,001
Platelet (/mm3)	243000 (IQR = 144500)	256000 (IQR = 155250)	233000 (IQR = 135500)	0.852
Blood creatinine (mg/l)	8.78 (IQR = 5.52)	9.02 (IQR = 6.22)	8.08 (IQR = 4.34)	0.226
CRP (mg/l)	206.97 (IQR = 160.45)	214 (IQR = 159.5)	192 (IQR = 161.49)	0.203
Procalcitonin (pg/l)	0.4 (IQR = 1.26)	0.485 (IQR = 1.43)	0.34 (IQR = 1.04)	0.003
Leukocytes (/mm3)	10980 (IQR = 7385)	11275 (IQR = 7270)	10460 (IQR = 7460)	0.434
Blood glucose (g/l)	1.51 (IQR = 1.14)	1.54 (IQR = 1.25)	1.5 (IQR = 1.08)	0.665
Lymphocyte (/mm3)	780 (IQR = 627)	755 (IQR = 640)	790 (IQR = 660)	0.007
Imagerical findings	183 (16.4%)	85 (7.6%)	98 (8.8%)	< 0,001
0–25%	170 (15.3%)	70 (6.3%)	100 (9%)	
25–50%	358 (32.1%)	232 (20.8%)	126 (11.3%)	
50–75%	403 (36.2%)	280 (25.1%)	123 (11%)	
75–100%				
Arterial Blood Gaz	7.44 (IQR = 0.13)	7.44 (IQR = 0.13)	7.43 (IQR = 0.12)	0.768
pH	34 (IQR = 7.38)	33.35 (IQR = 7.85)	35 (IQR = 8.6)	0.000
PaCO2 (mmhg)	58 (IQR = 22.75)	58 (IQR = 25.25)	59 (IQR = 20.05)	0.497
PaO2 (mmhg)	23.85 (IQR = 6.03)	23.4 (IQR = 6.05)	24.3 (IQR = 5.6)	0.514
HCO3- (mmol/l)	89 (IQR = 9)	89 (IQR = 10)	90 (IQR = 9)	0.38
SaO2 (%)	1.22 (IQR = 0.85)	1.2 (IQR = 0.92)	1.28 (IQR = 0.93)	0.3
Lactate (mmol/l)				

	Whole population (N = 1124)	Placebo (N = 412) Groupe A	Aspirin use (N = 712) Groupe B	pValue
Management	580 (52%)	122 (30.2%)	458 (64.3%)	< 0,001
Methylprednisone	211 (18.9%)	89 (22%)	122 (17.1%)	0.028
Dexamethasone	191 (17.1%)	56 (13.9%)	135 (19%)	0.017
Tociluzimab	14 (1.3%)	1 (0.1%)	13 (1.2%)	0.016
Plasmapherese	572 (51.3%)	185 (16.6%)	387 (34.7%)	0.004
Prone position	764 (68.5%)	302 (27.1%)	462 (41.4%)	< 0,001
High oxygen concentration	538 (48.2%)	206 (18.5%)	332 (29.7%)	0.09
high flow oxygen therapy	74 (6.6%)	41 (3.7%)	33 (3%)	< 0,001
CPAP	266 (23.6%)	138 (33.5%)	131 (18.4%)	< 0,001
Non invasive ventilation				

2) Primary and secondary end point

For the primary outcome of all-cause in-hospital death, 367 patients died with 165 in the placebo group and 202 in the aspirin group with a highly significant difference (p = 0. 001), for the secondary composite outcome, 104 patients had a thromboembolic event (limb ischemia, ischemic stroke, myocardial ischemia, pulmonary embolism or venous thrombosis) with 51 in the placebo group and 53 in the aspirin group with a significant difference. For the use of mechanical ventilation, 310 patients were intubated, with 189 in the asiprin group and 121 in the placebo group, but with no difference between the two groups, and finally for the use of ECMO, 30 patients had recourse to this assistance with 16 in the placebo group and 14 in the aspirin group with a significant difference (p = 0.039). (Table 2 summarizes the comparative results between the two groups with respect to the primary and secondary composite outcome).

Table 2
Comparative results between the two groups for the primary and secondary composite outcome

	Whole population (N = 1124)	Placebo (N = 412) Groupe A	Aspirin use (N = 712) Groupe B	pValue
Primary outcomes Death (%)	367 (32.65%)	165 (40%)	202 (28.4%)	**< 0,001**
Secondary composite outcomes	104 (9.3%))	51 (4.6%)	53 (4.8%)	**0.005**
Thrombo-embolic events (%)	54 (4.8%)	21 (1.9%)	33 (4.6%)	0.391
CIVD (%)	310 (27.8%)	121 (10.8%)	189 (16.9%)	0.125
Mechanical ventilation (%)	30 (2.7%)	16 (1.4%)	14 (1.3%)	**0.039**
ECMO (%)				

3) Aspirin use benefit

In order to know the benefit of aspirin on the primary outcome, and after a Cox regression analysis adjusted to the variables described in the literature, we find that the use of asprin has a beneficial effect on intra-hospital mortality with HR = 0. 691 (95%CI: 0.541–0.882) since it allows a 30% reduction in mortality (Fig. 1), and this reduction varied between 20 and 50% (p = 0.003), on the other hand the use of ventilation remains a predictive factor of mortality with HR = 2.75 (95%CI 2.202–3.453) (Table 3)

Table 3
Cox proportional hazards regression analysis for predicting mortality

Variables	Hazard-ratio	95% CI	pValue
Age	1.003	0.995–1.010	0.872
Cardiovascular disease	0.805	0.593–1.093	0.104
D-Dimers	1.24	1.291–2.291	0.792
Mechanical ventilation	**2.75**	2.202–3.453	**< 0,001**
Aspirin use	**0.691**	0.541–0.882	**0.003**

For the secondary outcome, aspirin reduced exposure to thromboembolic events by 55%, and this reduction varied between 18% and 72% (95% CI 0.279–0.719) (p = 0.001) (Table 4 - Fig. 2). For the use of mechanical ventilation, in univariate analysis, there was no significant difference between the two groups, for this, we deduce that aspirin did not allow a rehabilitation of the rate of intubation for our patients.

Table 4
Cox proportional hazards regression analysis for predicting thrombo-embolic events

Variables	Hazard-ratio	95% CI	pValue
Age	1.092	1.001–1.035	**0.036**
Cardiopathie	0.802	0.493–1.727	0.802
D-Dimers	2.706	0.932–1.729	0.706
Fibrinogen	1.892	0.786–1.012	0.075
ECMO	2.616	0.628–10.898	0.187
Aspirin use	0.448	0.279–0.719	**0.001**

Discussion

In the literature, the published results in this sense remain controversial regarding the effect of the use of asprin on intra-hospital or 30-day mortality. Starting with the randomized, controlled, open-label trial of 7541 patients [9], with the primary outcome of all-cause death, there was no significant difference in 28-day mortality between the two groups (aspirin versus placebo), and for the secondary composite outcome (use of invasive ventilation, renal replacement therapy and 28-day discharge rate), only the 28-day discharge rate had a significant difference (RR = 1. 06; 95% CI 1.02–1.10;p = 0.0062) between the two groups. In a meta-analysis conducted by Shaodi et al on 49041 patients [10], on the benefit of asipine on the risk of mortality, a beneficial effect was found (RR 0.78; 95% CI 0.61–0.97; P = 0.03; adjusted RR 0.73; 95% CI 0.52–0.99; P = 0. 04) but the main limitation of this meta-analysis is the very high heterogeneity (I2 = 90%), another meta-analysis performed in the same direction but this time including only 1054 patients conducted by Mehta et al [11] did not find a benefit for the use of aspirin on mortality (RR = 1.43 and p = 0.4). In a large French cohort of 31 million [12] patients with no history of heart disease, there was no benefit of low-dose aspirin use on mortality or on the use of mechanical ventilation. Given this convergence of results, we must wait for the results of the ongoing trials on the effect of aspirin on the progression of the disease (ACTCOVID19; NCT04324463 and LEAD COVID-19; NCT04363840) [13], in order to have an equally objective idea of the degree of benefit of aspirin on the prevention of mortality.

Regarding the prevention of thromboembolic events, according to a large cohort of a Spanish registry of 21962 patients hospitalized for severe infection with COVID-19, there was no protective effect of aspirin on venous thromboembolic events [14], adding to this study, a cohort of 22072 patients, whose main objective was to determine the benefit of aspirin use on thromboembolic events, carried out by aditya et al[15], paradoxically showed a negative effect of aspirin on this outcome with a higher percentage in the aspirin group (9. 3% aspirin vs 2.8% no aspirin; p = 0.005). In our study, we observed a protective effect on mortality and thromboembolic events but no effect on the use of mechanical ventilation, and for this

convergence of results between the different studies, we need more controlled, randomized, double-blind trials to be able to make a relevant recommendation on the benefit of aspirin use.

The Limitations

Like most studies, our study has some limitations, mainly the number of patients, although it is high, but given the discrepancy of published results, it is better to have a larger number, adding to this, that the follow-up for the primary and secondary outcome of our patients is limited just during the duration of hospitalization, and we have not studied these results in the medium and long term.

Conclusion

Pending the results of other studies, and ongoing trials on the benefit of aspirin in COVID-19 patients, this therapeutic decision remains controversial and practitioner dependent due to the absence of guidlines to date.

Declarations

Authors' Contributions:

- G. Elaidouni and A. Bouchlarhem: contributed to the conception and design of the study, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.
- H. Bkiyar, N. Ismaili, N. Elouafi and B. Housni: supervision and manuscript validation.

Funding: This study was nofunded.

Data Availability: None

Code availability: None

Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Ethical Approval: All procedures performed in studies involving human participants were following the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declarationand its later amendments or comparable ethical standards. And approved From Mohammed Ith University ethical committee for biomedical research in OUJDA (Morocco) under the number **017/20.**

Informed Consent: For both groups, an informed consent was presented to each patient upon admission, for the explanation of the interest of the study, and the potential benefit expected as well as the complications on the use of aspirin. All included patients granted their participation in the study, with a signed consent. Data anonymity was respected in accordance with national and international guidelines

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Figures

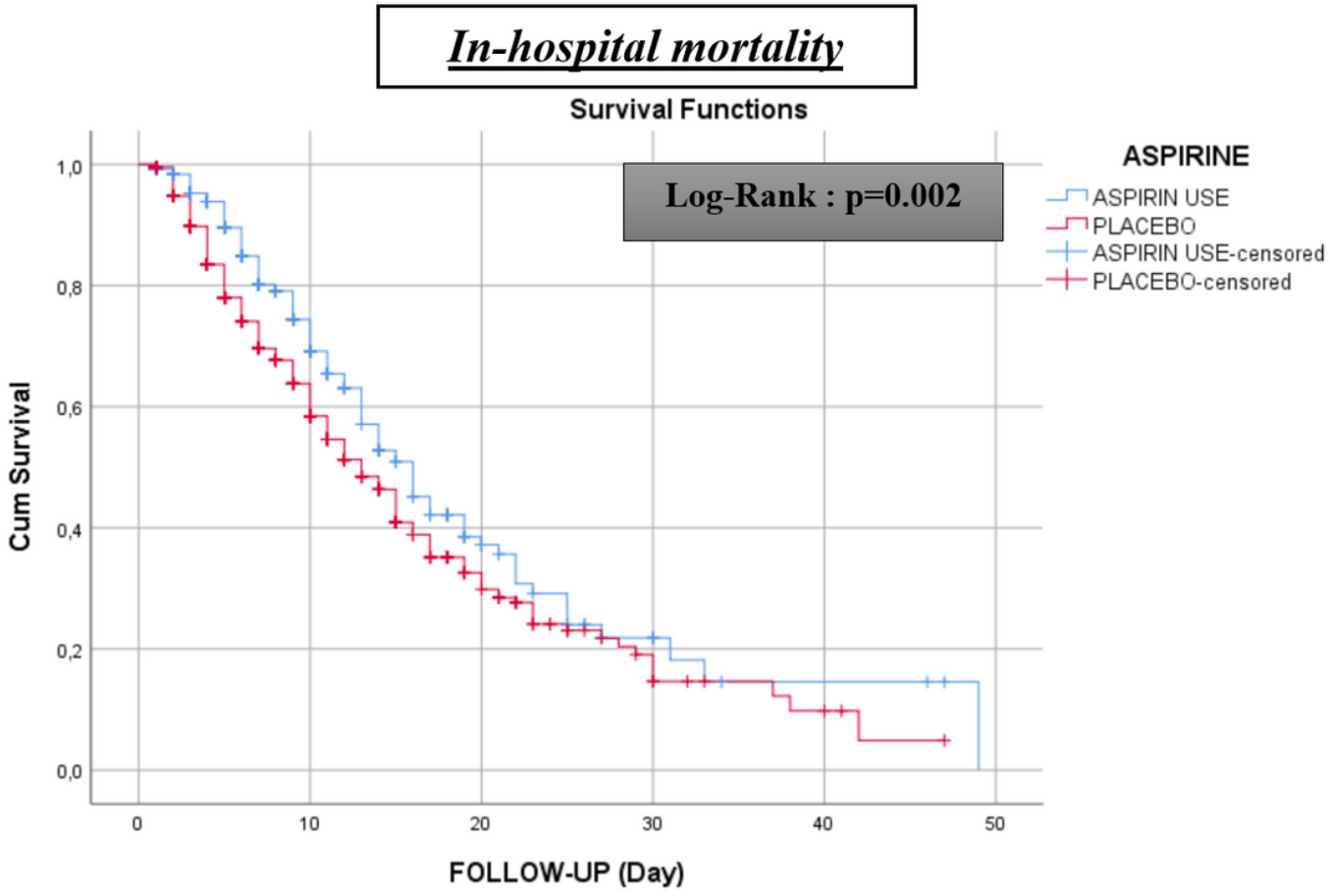

Figure 1

kaplan meirer survival curve showing the significant difference of aspirin use on mortality

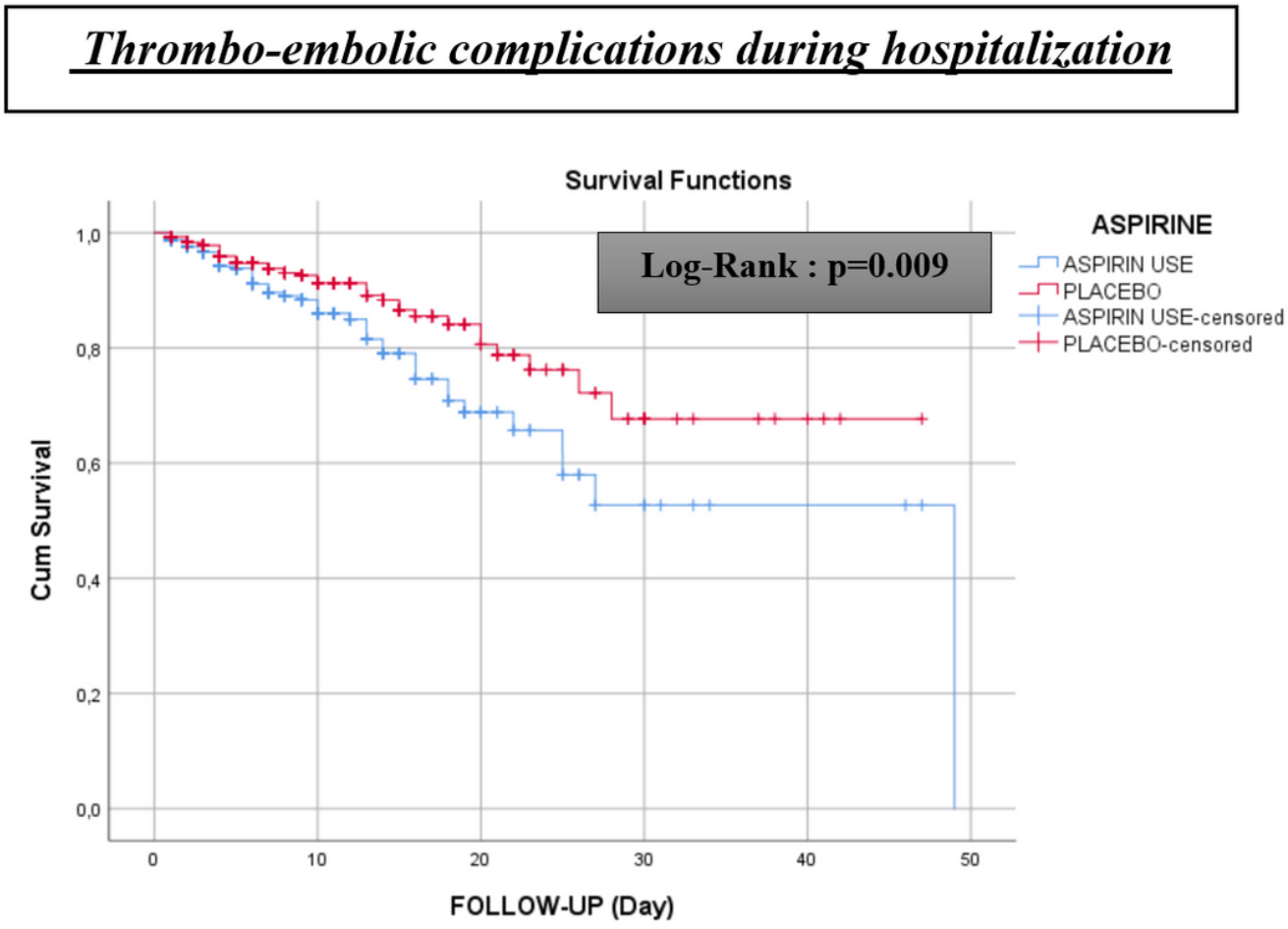

Figure 2

kaplan meirer survival curve showing the significant difference of aspirin use on thrombo-embolic events