Beneficiary outcomes of abciximab in COVID-19 patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention.

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Abstract

Background: SARS CoV2 pandemic affected the whole world with a high thrombotic burden during ST-segment elevation myocardial infarction (STEMI of the acute coronary syndrome. Meta-analysis and previous data have shown about GP2b3a inhibitor (Abciximab) has short and long-term efficacy in patients with STEMI undergoing PCI with high thrombotic burden.

Objectives: It was performed to verify the short-term & long-term efficacy and safety of abciximab in patients with STEMI undergoing percutaneous coronary intervention (PCI) during the COVID-19 era.

Method: We conducted a multicentre cross-sectional observational study in north India among 433 patients of ACS presented STEMI with SARS CoV2 RT PCR positive cases followed by PCI with DES drug-eluting stents.Meta-analysis and systematic review equated with or without abciximab in STEMI with PCI.We divided into two groups: A (with abciximab) n=197 and B (without abciximab) n=236 during PCI.

Result: Results found in group A versus B about significant differences in risk of 30 days mortality (RR 0.51, CI 0.13–1.95, p =0.034) but major bleeding (1.17, 0.63–1.71, p =0.042), and transfusion (1.21, 0.94–1.61,) between the two groups. However, there were significant differences in risk of mortality at 6 months (0.40, 0.14–0.66,p=0.034), and mortality at 12 months (0.43, 0.22–0.64,p=0.013). At the 12month follow up showed MACE rate (0.51, 0.43–0.72,p=0.023), recurrent myocardial infarction (0.54, 0.23–0.85, p=0.053), repeat revascularization (0.57, 0.33–0.81, p=0.041),minor bleeding (1.28, 1.12–1.44, p=0.051), and thrombocytopenia (1.84 1.30–2.07, p=0.048).

Conclusion: The role of abciximab could lead to a lower risk of reinfarction, revascularization, and all-cause death but a higher risk of minor bleeding, and thrombocytopenia during COVID 19 era.

Keywords: - Acute Coronary Syndrome, STEMI, COVID-19, Abciximab, PCI

Abbreviations:

1. SARS –severe acute respiratory syndrome
2. CoV2 – Corona Virus -2
3. STEMI – ST-elevation myocardial infarction
4. GP2b3a – Glycoprotein 2b3a
5. PCI – percutaneous coronary intervention
6. COVID-19– Corona Virusdisease -19
7. ACS – Acute coronary syndrome
8. RT PCR – Reverse transcriptase polymerase chain reaction
9. DES –Drug-eluting stent
10. MACE– Major adverse cardiovascular events
11. NSTEMI- Non-ST-elevation myocardial infarction
12. LVEF– Left ventricle ejection fraction
13. DAPT– Dual Anti platelets therapy
14. PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-analysis
15. TIMI- Thrombolytic in myocardial infarction
16. RR- Risk Ratio
17. CI- confidence interval
18. TSA-Trial Sequential Analysis

19. TLR-Target lesion revascularization

1. Introduction:

As per universal data, acute coronary syndrome or myocardial infarction is a major cause of death across the globe. Recently SARS CoV2or Coronaviral disease (COVID-19) pandemic had higher mortality in ACS patients (STEMI/ NSTEMI) especially in the young generation due to more thrombotic burden.(1) Anti-platelet agents had shown their great contribution to got good outcomes after percutaneous coronary intervention (PCI).(2) Nowadays new antiplatelet agents like P2Y12 inhibitors (Ticagrelor,Prasugrel) with quick and sound effects have decreased the use of glycoprotein IIa/IIIb inhibitors like Abciximab in patients with STEMI. (3,4)

However, data suggest extra beneficial effects of Abciximab or other GP IIa/IIIb inhibitors in hemodynamic ally compromised STEMI patients or orally anti-platelet agents might fail or could not give before primary STEMI or need of intravenous agent due to prompt action in high thrombotic burden to prevent further complications.(4)

An additional role of abciximab has been reported before primary PCI compared to per-procedural use in a typical manner in STEMI patients. Previous studies have shown there was not too much difference between intracoronary and intravenous administration of abciximab in STEMI patients during PCI.(4) As we know platelets have a master key role in the path physiology of ACS patients with thrombotic complications before, during, and after PCI. Some unfavorable conditions or high thrombotic situations with other co-morbidities associated with the same during complex coronary interventions require GP IIa/IIIb inhibitors, especially abciximab, a Fab fragment of the chimeric murine human monoclonal antibody 7E3. It prevents the binding of fibrinogen, von Willebrand factor, and other agents to GP IIa/IIIb receptors on activated platelets resulting inhibition of platelet aggregation.(4,5)

2. Methods:

2.1 Study design:

The multicentrecross-sectional observational study in north India. This study was accomplished to verify the short-term & long-term efficacy and safety of abciximab in patients with STEMI undergoing primary PCI during the COVID-19 era.

2.2 Study Criteria:

(1) STElevation MI defined clinically with insistent myocardial ischemia symptoms and electrocardiographic signal but without angiographic selection criteria, (2) The reperfusion therapy with PCI, (3) Data comparison of patients with or without abciximab (4) It was reported the risk of mortality at 30 days,6 months and 12 months. The exclusion criterion of the study included nonrandomized controlled trial and observation studies, as well as patients with non-STEMI.

2.2a Inclusion Criteria:

Age- 19 to 65 years	ECG- STEMI
LVEF > 30%	SARS COV2 +VE
Good Hemodynamic Status	Consent- Taken

2.2b Exclusion Criteria:

Bleeding disorders	Hematological disorders
Thrombocytopenia	Cirrhosis of the Liver, Portal Hypertension
Dengue, Malaria, Typhoid fever	Hypersensitivity
Pulmonary hemorrhage	Inflammatory Bowel Disease
Intracranial hemorrhage	Recent Major Surgery
>Grade 2 Hypertension	Pregnancy
Pediatric group	Geriatric Group

2.3 Ethical Committee Approval and Consent:

We discussed this study with the hospital administration and ethical committee for additional benefits of abciximab and granted approval for the same. We have filed with patients' authentic consent regarding this medicine to reduce mortality and adverse cardiovascular events.

2.4 Data Collection:

We conducted a multicentric cross-sectional observational study in north India among 433 patients of ACS who presented STEMI with SARS CoV2 RT PCR positive cases followed by percutaneous coronary intervention with DES drug-eluting stents. We divided into two groups: A (with abciximab) n=197 and B (without abciximab)

n=236 during PCI. In this study about abciximab, a single bolus with a dose of 0.25 mg/kg was followed by a continuous intravenous infusion of 10 µg/min for the time duration of 12 to 24 hours.Both groups had the same optimized medical therapy like DAPT (Aspirin plus ticagrelor)and a high dose of statin. All patients were ruled out for serious comorbid conditions.

We tried to enroll the homogenous variables among both groups prior to starting the study, we can see the table-1. The fixed-effects model calculated the relative risk (RR) and 95% confidence intervals (CI) of outcomes. Systematic review and meta-analysis compared with or without abciximab in patients with STEMI undergoing PCI.

2.5 Data Analysis:

Extraction and analysis of data followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [4]. The baseline characteristics of patients and trials were extracted by 2 researchers independently, and the divergences were resolved through negotiation. The primary efficacy outcomes consisted of mortality at 30 days, 6 and 12 months, recurrent MI, repeat revascularization, and final thrombolysis in myocardial infarction (TIMI) flow <3.The primary safety outcomes included bleeding (major or minor) and thrombocytopenia.

This meta-analysis was used by Review Manager Version 5.4 software (The Nordic Cochrane Center, Copenhagen, Denmark), and the Cochrane *Q* statistic with Pearson chi-square test and the Higgins I^2 test was performed to assess heterogeneity in Review Manager Two-tailedvalues were exploited for all results, and statistical significance was set at Trial Sequential Analysis (TSA) version 0.9.5.10 software was used to estimate the sample size of statistical differences in each outcome (based on an α of 0.05 and a power of 0.8). Moreover, Egger's and Begg's tests and visual inspection of funnel plots were employed to assess publication bias.(4)

Table 1: Different variables of both groups (a-Abciximab and b- without Abciximab) at the initial phase of the Study.

Variables	Abciximab Group	Normal Group	P Value
Numbers	N=197	N=236	0.027
Male	121(61.4%)	139(58.9%)	0.032
Female	76(38.6%)	97(41.1%)	0.042
Hypertension	83(42.1%)	104(44.1%)	0.032
Diabetes	66(33.5%)	89(37.7%)	0.039
Thyroid	19(9.6%)	25(10.5%)	0.022
SBP mmHg	155+/-11	148+/-13	0.032
DBP mmHg	93+/-8	95+/-11	0.046
HR beats/min	104+/-15	98+/-17	0.032
RR rate/min	34+/-10	31+/-11	0.055
Temp degree F	100.7+/-1.1	99.6+/-1.2	0.032
Spo2 %	92+/-11	93+/-11	0.023
ECG ST elevation mv	3.5+/-1.2	3.2+/-1.1	0.021
LVEF %	56+/-14	58+/-15	0.032
LDL mg/dl	163+/-11	154+/-11	0.045

HDL mg/dl	45+/-8	43+/-9	0.032
CRP mg/dl	28+/-7	26+/-8	0.038
D-Dimer g/L	0.92+/-0.13	0.88+/-0.21	0.032
IL-6pg/ml	89+/-23	83+/-17	0.053
Trop-I ng/ml	4.63+/-1.21	3.93+/-2.12	0.032
RBS mg/dl	183+/-31	190+/-28	0.056
Sr. Creatinine mg/dl	1.43+/-0.5	1.32+/-0.6	0.028

3. Results:

Primary Outcomes-

Our study found a significant difference in primary outcomes, short-term as well as long-term which favors the abciximab group, as per results mortality at 30 days revealed in the abciximab group 3.2% v/s 5.1 % in the normal group with significant p-value 0.032. On the other hand, regarding the long-term benefits of abciximab at the same aspect mortality at 6 months & 12 months (4.3% v/s 6.8 % p-value 0.041 and 5.0% v/s 8.1 % p-value 0.057) which could favor to abciximab group. (**See the figure-1)**

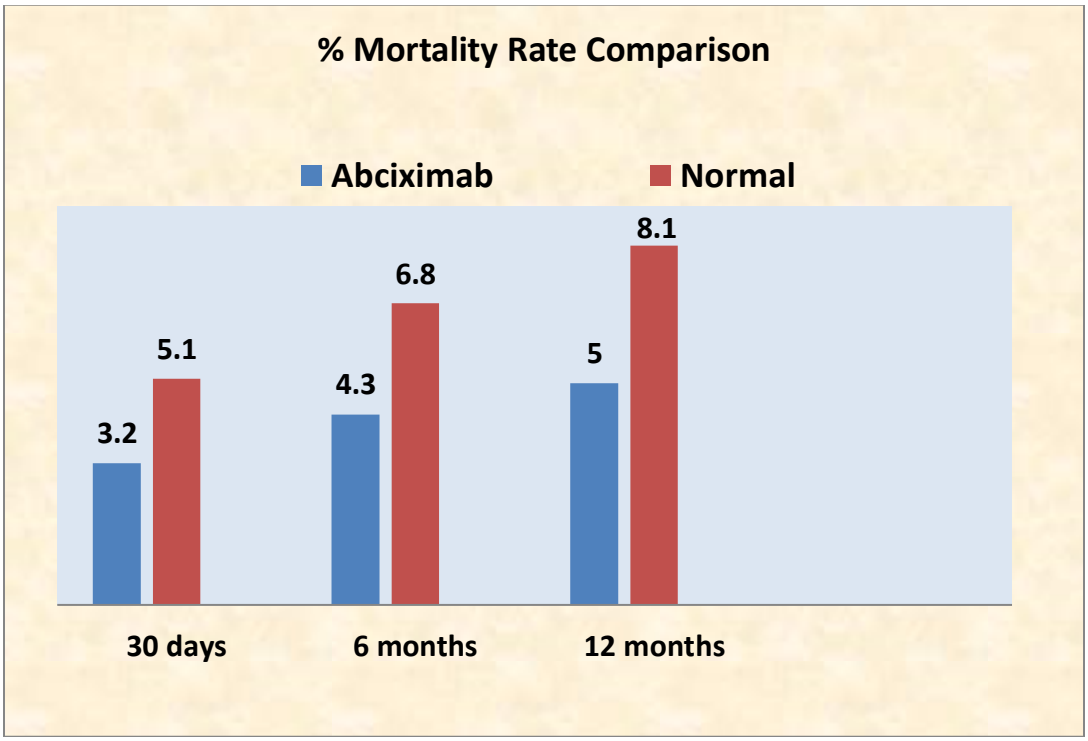

Figure-1 Short-term and long-term mortality difference between both groups.

Results found in group A versus B about significant differences in risk of 30 days mortality (RR 0.51, CI 0.13–1.95, p =0.034) but major bleeding (1.17, 0.63–1.71, p =0.042), and transfusion (1.23, 0.94–1.61, P=0.045) between the two groups. However, there were significant differences in risk of mortality at 6 months (0.40, 0.14–0.66, p=0.034), and mortality at 12 months (0.43, 0.22–0.64,p=0.013) with high survival rate in the abciximab group (see the figure-2). Our data showed about bleeding rate was a little bit on the higher side of the abciximab group, however, the major bleeding rate was not significantly high in the abciximab group as compared to the normal group (4.1% v/s 3.9 %, p-value 0.044**(see the figure-3 & Table-2).**

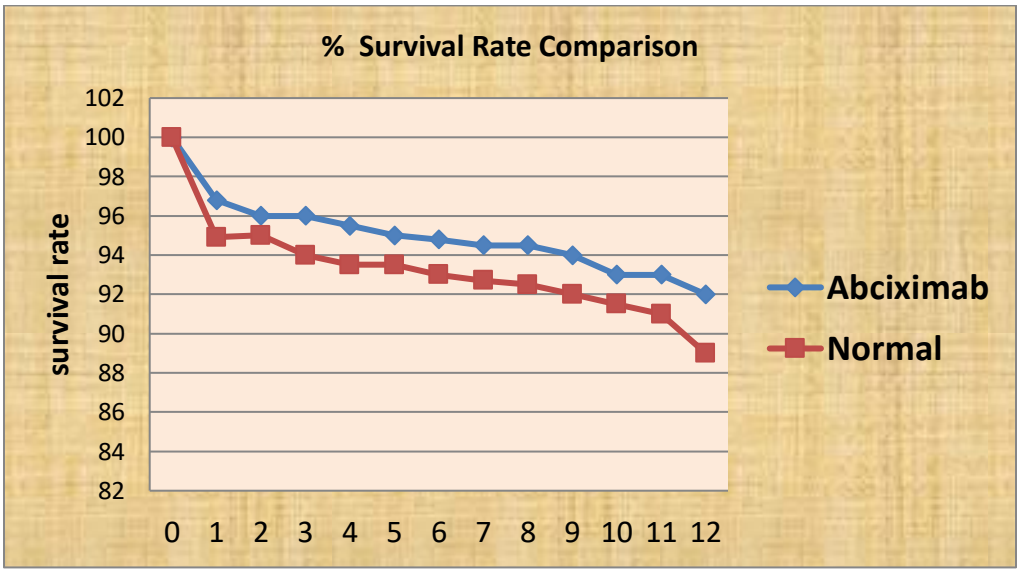

Figure-2 Survival rate comparison

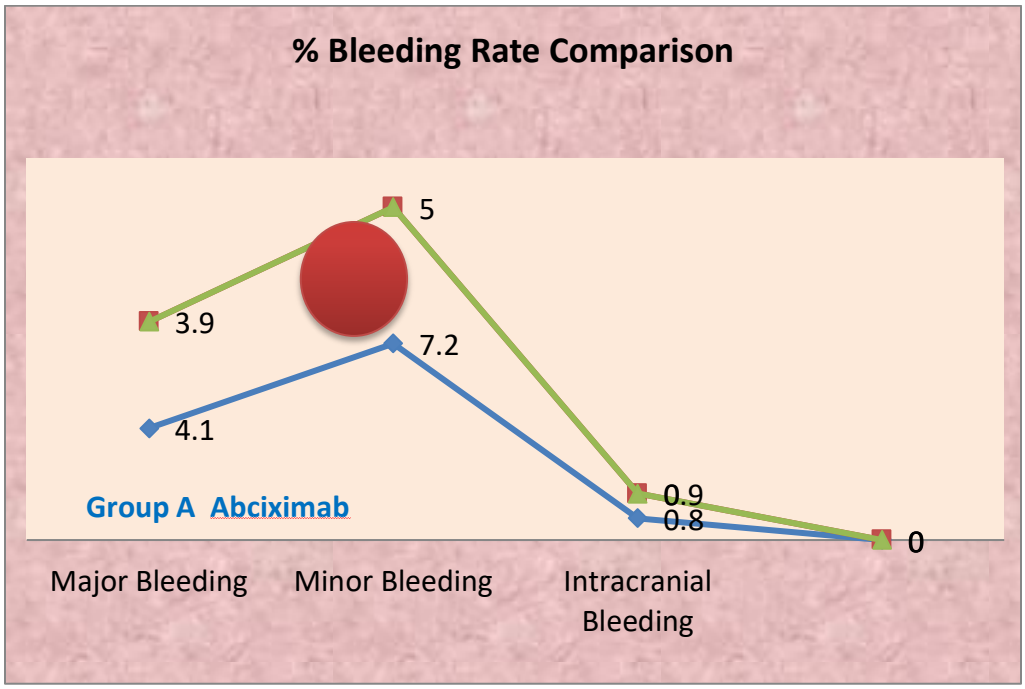

Figure-3 Bleeding rate comparison.

Table 2: Different variables of Both groups (a-Abciximab and b- without Abciximab) at the initial phase of the Study.

Variables	Abciximab Group	Normal Group	P Value
Primary Outcomes			
Mortality			
30 days	3.2%	5.1%	0.032
6 months	4.3%	6.8%	0.041
12 months	5%	8.1%	0.057
Secondary Outcomes			

Long Term Outcomes			
MACE	4.5%	7.4%	0.042
Infarct Size reduction	2.4%	1.9 %	0.039
Survival Rate	94%	91%	0.030
Restenosis	1.7 %	2.6 %	0.052
Repeat Revascularization	3.5 %	5.1%	0.047
Clinical Improvement	89 %	83 %	0.031
LVEF Improvement	13.0+/-5%	9. 0+/-4%	0.037
Bleeding			
Major bleeding	4.1%	3.9%	0.042
Minor bleeding	7.2%	5.0%	0.036
Intracranial bleeding	0.8%	0.9%	0.055
GI bleeding	1.2%	1.1%	0.043
Thrombocytopenia	5.3%	3.9%	0.038

Secondary Outcomes-

The current study found positive secondary outcomes in the abciximab group as compared to the normal group. There was a significant improvement in infarct size reduction in the abciximab group versus the normal group (2.4 % v/s 1.9 %, p =0.039), and less restenosis (1.7 % v/s 2.6 %, p =0.052)**.(see figure-4 & table-2)**

On the other hand, in the abciximab group, significantly lower repeat revascularization rate (3.5 % v/s 5.1 %, p =0.047)and MACE rate (4.5 % v/s 7.4 %, p =0.042)as compared to the normal group after 12 months follow up. **(see figure-4 & table-2)**

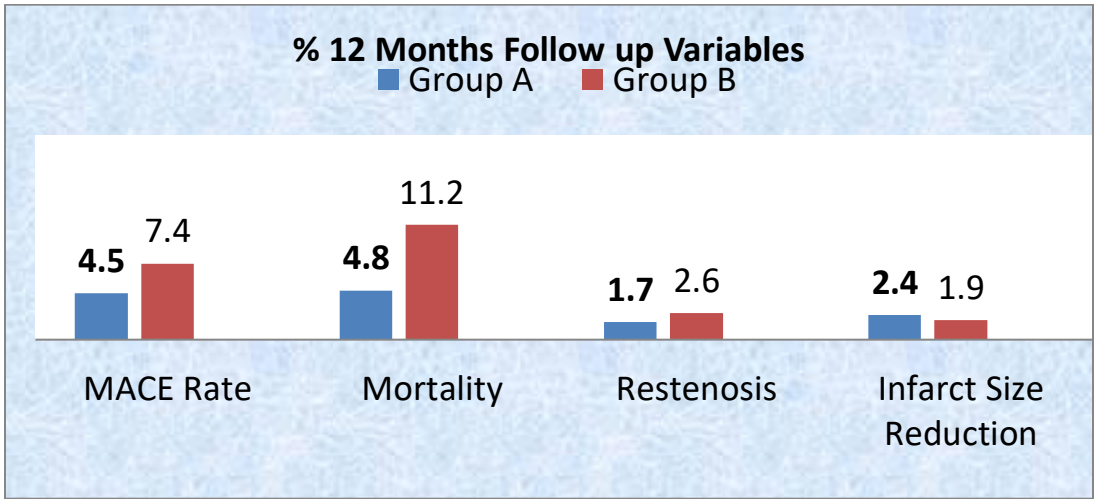

Figure-4 Long term variable comparison at 12 months.

At the 12month follow up showed MACE rate (0.51, 0.43–0.72,p=0.023), recurrent myocardial infarction (0.54, 0.23–0.85, p=0.053), repeat revascularization (0.57, 0.33–0.81, p=0.041),minor bleeding (1.28, 1.12–1.44, p=0.051), and target lesion revascularizationTLR (0.63, 0.33–1.18, p=0.039),thrombocytopenia (1.84 1.30–2.07, p=0.048).

Adverse reactions- (see the table-3)

Table 3: Adverse Drug Reactions Among Treated Patients with or without abciximab

Variables	Abciximab Group	Normal Group
Bleeding		
Major bleeding	4.1%	3.9%
Minor Bleeding	7.2%	5.0%
Cardiac disorders		

Bradycardia	5.1%	4.7%
Gastrointestinal disorders		
Nausea	14.8%	12.5%
Vomiting	8.3%	6.5%
General disorders and administration site conditions		
Chest pain	12.4%	9.2%
Puncture site pain	4.6%	3.8%
Abdominal pain	4.1%	3.2%
Musculoskeletal and connective tissue disorders		
Back pain	18.5%	14.5%
Nervous system disorders		
Headache	7.3%	6.5%
Vascular disorders		
Hypotension	15.3%	11.3%
Peripheral edema	1.7%	1.2%
Cardiac disorders		
Tachycardia	2.5%	1.8%
others		
Giddiness	11.6%	8.5%
Vertigo	6.3%	4.8%

4. Discussion:

The COVID-19 pandemic with heavy SARS CoV2 load has shown an additional thrombus burden in ACS patients, especially in STEMI patients which may cause a high rate of re-stenosis, MACE, and mortality.(1,2) Previous works of literature have shown the abciximab **(see Figure-5)**(5,6)

FIGURE-5 ABCIXIMAB – CLINICAL PHARMACOLOGY- AT A GLANCE

ABCIXIMAB – CLINICAL PHARMACOLOGY- AT A GLANCE	
Mechanism of Action	**Pharmacodynamics**
Fab fragment of the chimeric monoclonal antibody 7E3. Selectively binds to the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor located on the surface of human platelets. Inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor, and other adhesive molecules to GPIIb/IIIa receptor sites on activated platelets. Also binds with similar affinity to the vitronectin ($\alpha_v\beta_3$) receptor which mediates pro-coagulant properties of platelets and proliferative properties of vascular endothelial cells and smooth muscle cells.	Intravenous administration or Intracoronary administration Single bolus dose of 0.25 mg/kg followed by a continuous infusion of 10 µg/min for periods of 12 to 96 hours produced sustained high-grade platelet inhibition. Platelet aggregation in response to 5 or 20 µM ADP less than 20% of baseline and bleeding time greater than 30 minutes for the duration of the infusion in most patients. Equivalent results were obtained when a weight-adjusted infusion dose (0.125 µg/kg/min to a maximum of 10 µg/min) was used in patients up to 80 kg.
Pharmacokinetics	***Contraindications***

Free plasma concentrations decreased very rapidly with an initial half-life of several minutes and a second phase half-life of about 30 minutes. Disappearance from the plasma is probably related to rapid binding to the platelet GPIIb/IIIa receptors (approximately 80,000 to 100,000 GPIIb/IIIa receptors on the surface of each platelet). After a single bolus injection inhibition of platelet aggregation, was evident within 10 minutes. The antibody remains in circulation for 15 days or more in a platelet-bound state. Its disappearance follows a mono-exponential course. Total plasma concentrations from the first time point measured (usually 2 hours) for all infusion rates and durations. At the termination of the infusion period, plasma concentrations fell rapidly for approximately 6 hours, then declined at a much slower rate	Active internal bleeding Recent (within six weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance. History of cerebrovascular accident (CVA) within two years, or CVA with a significant residual neurological deficit Bleeding diathesis Administration of oral anticoagulants within seven days unless prothrombin time is ≤ 1.2 times the control Thrombocytopenia (< 100,000 cells/μL) Recent (within six weeks) major surgery or trauma Intracranial neoplasm, arteriovenous malformation, or aneurysm Severe uncontrolled hypertension Presumed or documented history of vasculitis Use of intravenous dextran before PCI, or intent to use it during an intervention

and its beneficial role in primary PCI with a high thrombotic burden. The authors of this study could implementthe beneficial use of abciximab can reduce the chances of distal embolization followed by boosting the effect ofmyocardial perfusion, hence it might be the cause of long-term good outcomes. Previous research studies have shown that distal embolization is associated with myocardial insufficiency, large infarct size, lower LVEF, frequent hospitalization, and mortality rate. The major adverse cardiovascular events like recurrent myocardial infarction, TIMI flow <3 and recurrent revascularization was significantly reduced by 43%, 22%, and 41%. The meta-analysis reveals the relative risk reduction of all-cause death at 30 days and 6 months was 22% and 41%, separately.(4,5,6)

Previous clinical data have shown that distal embolization is relatedto larger infarct size, lower LVEF, and higher risk of mortality [4,8]. The submission of abciximab can decrease the formation of distal embolization and improve myocardial perfusion, thus fetching long-term benefits [4,9]. Still, less than 20% of patients with distal embolization can be documented during angiography [17]. United with the additionalmutualdifficulties of distal embolization in patients with previous MI, anterior wall MI and multivessel diseases, the application of abciximab in this sub-population may be beneficial [17]. Moreover, it is blurred how it is affected by the dual antiplatelet drugs currently used. Hence, it is essential to further collect dataon whether the combination of abciximab on the basis of dual antiplatelet will profit patients who may have distal embolization. About RR (risk ratio) of recurrent MI, final TIMI flow <3 and repeat revascularizationwas significantly reduced by 43%, 21%, and 41%, correspondingly, which had significant clinical benefits. Though, the curve of recurrent MI and final TIMI flow (<3) did not overdo the TSA limit, which validates more randomized controlled trials are needed to light the anticipated sample size.(4,10) This study revealed significant risk reduction of MACE rate at 12 months as compared to other studies which have been published. (See figure-6 meta-analysis)

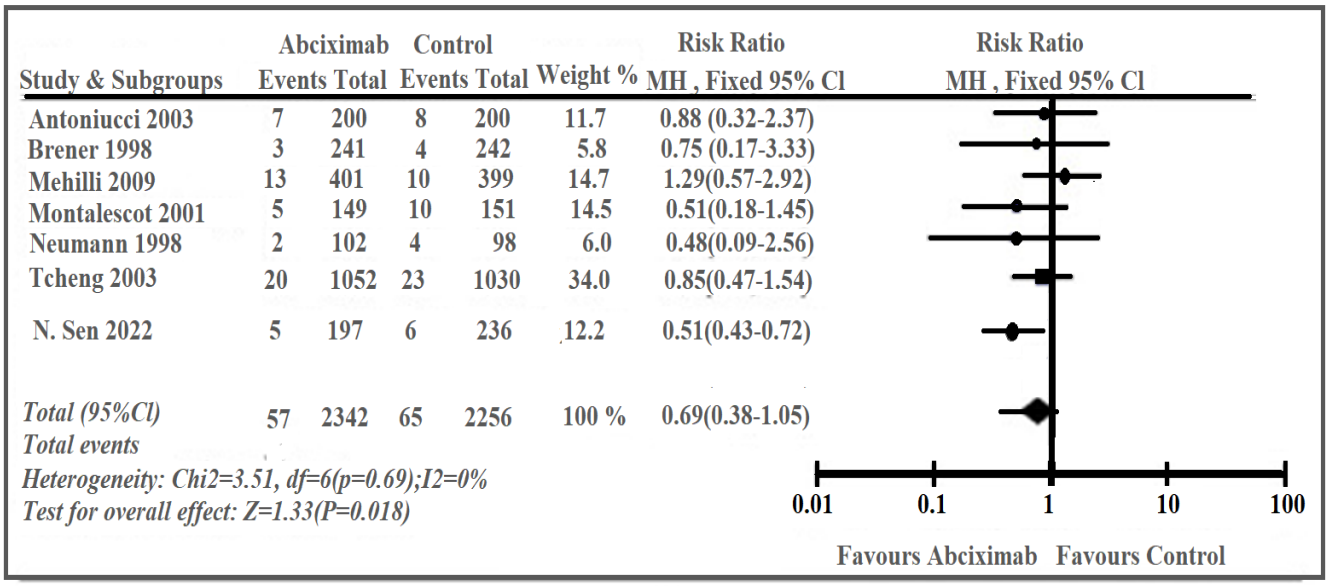

Figure-6 Meta analysis of MACE rate effective graph at 12 months comparison.

The study revealed that, compared with the control group, the risk ratio of major bleeding in the abciximab group was augmented by 17 %. Comparable to the result of another meta-analysis, abciximab can raise the possibility of major bleeding [9,10]. The rate of transfusion was privileged in the abciximab group, but there was no noteworthy difference. Even though the indications of transfusion were not acknowledged in most of the trials included, the transfusion was directly linked with major bleeding in the trial conducted by Ernst et al. [12]. Allowing for moderate heterogeneity was pragmatic in minor bleeding ($I^2 = 63\%$), the sensitivity study was advance performed and the CADILLAC trial is measured to be the main reason of heterogeneity [15]. While the results of this meta-analysis come from precise situations and populations. The outcome are different from previous studies of patients with these diseases [10, 17], and the submission of abciximab was recommended only in early coronary intervention in STEMI patients [17]. Alternatively, the molecular composition of abciximab is dissimilar from the other two GPIs (tirofiban and eptifibatide) [18]. Various trials in which tirofiban was not inferior to abciximab have strained different conclusions [20, 21].

Nowadays, the management of ACS patients with STEMI is mandatory to make a proper system to diagnosis early and to transfer rapidly for primary PCI at capable centers; choice of optimal supportive pharmacotherapy (timing and model of abciximab management), finally, PCI procedure with enthusiastic devices.(4) It may decrease the clinical events rate, especially mortality, in patients with STEMI withhigh risk. So, the literature recommends the discerning use of abciximab for high-risk of ischemic events (large thrombus burden,large anterior wall infarction,) and/or angiographic complications (no reflow, distal embolization,) of primary PCI. (7,13,14) An additional role of abciximab in patients with STEMI pre-managed with new $P2Y_{12}$ inhibitors, which are becoming extra popular, is not so far appropriately defined. Commonly intravenous route of application of the abciximab is recommended as per the literature, however, the intracoronary route may be judicious, with possible intralesional submission in patients of STEMI with a very large thrombus consignment at the site of occlusion. (7) To progress safety outcomes of the application of abciximab, the practice of a radial route should be sturdily well-thought-out in patients of STEMI undergoing primary PCI.In extra-positive play role of the abciximab may be in the projected delayed onset of action of oral antiplatelet drugs (unstable hemodynamics, cardiogenic shock, hypothermia, and cardiac arrest).(4, 5, 20, 21)

5. Limitations

We could not enroll the large sample size due to standard national protocol for COVID-19 patients, this was the primary limitation of our study. Secondly, we received about 40 % of patients from rural or semi-urban areas where STEMI patients were diagnosed early. We tried to get accuracy at the homogenous part of pharmacotherapy with the uses of heparin along with abciximab or not. However, how much doses of heparin or enoxaparin were given, was exactly unknown to us in a real platform. Our study included meta-analysis is relatively old, and there is inadequate evidence of the outcome of abciximab in a dual antiplatelet framework. Hence, more clinical studies or trials are required to confirm the efficacy of the same in this era.

6. Future Aspect:

- More studies and trials are required.

- More clinical implementation is required in those situations related tothe high thrombotic burden.
- May be additional protocol drugs during PCI with COVID-19 like a pandemic.

7. Conclusion:

Our cross-sectional study on COVID-19 patients with systematic review and meta-analysis justifies that abciximab has an association with a lower risk of short-term all-cause death with good long-term outcomes, recurrent MI or restenosis, repeat early revascularization, and improved myocardial perfusion in STEMI patients undergoing PCI but a higher risk of minor bleeding and few incidences of thrombocytopenia. However, the risk of major bleeding may be pleased by electingticagrelor or clopidogrel rather than ticlopidine. Early or prompt administration of the abciximab could be beneficial in STEMI patients with high thrombotic burden situations like the COVID-19 pandemic or coming same disasters.

8. Acknowledgment:

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9. Conflict of interest:

None about any funding and disclosure.

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