Beta-Blocker Treatment in Ventilated COVID-19 patients – A Cox Regression with Time Dependent Covariate Analysis

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Abstract

Background: Patients with co-morbidities are particularly vulnerable to severe COVID-19 disease. Critically ill patients with COVID-19 frequently experience severe tachycardias and avoidance of these is important in some co-morbidities, for instance cardiovascular disease. There is growing interest in beta blockade in critical illness as their use been associated with improved outcomes in a variety of conditions. We report the real-world use of heart rate management in patients during the first wave of the COVID-19 pandemic. As retrospective data are prone to an Immortal Time Bias, we created a Cohort Trial such as might be used for a future prospective trial and used Time Dependent Covariate Analysis for its analysis.

Methods: Data for all PCR-proven COVID-19 patients ventilated in the Intensive Care Unit (ICU) were extracted from the hospital databases. To compensate for the risk of immortal time bias, we restricted analysis to 144 patients who achieved a heart rate (HR) of 90 beats per minute for more than 12 hours and were treated with norepinephrine. We recorded time from these 'entry criteria' to first beta blocker dose. Those patients who did not receive a beta blocker were given a nominal time to beta blocker beyond the censor day. Outcome was mortality censored at 28 days.

Results: In the study group, 83/144 patients (57.6%) received a beta blocker. The median interval from entry criteria to beta blocker was 7.91 days (IQR 3.89, 13.15) and median duration of treatment was 7.00 days (IQR 4.00, 14.00). Twenty-four beta blocker patients (28.9%) died within 28 days compared with 29 (47.5%) who did not (adjusted OR 0.43; 95% CI 0.20-0.95, P=0.036). Cox Regression with time-dependent covariate analysis revealed there was an increased, but not significant, risk of death with beta blocker delay (Hazard Ratio 1.42 p=0.264). Mortality was also reduced for each day treated with beta blockade (adjusted Odds Ratio 0.76, 95% CI 0.64-0.91; P=0.002).

Conclusions: In a retrospective analysis of critically ill ventilated patients with COVID-19 who developed a tachycardia >90 beats per minute and were treated with norepinephrine, beta blockade was associated with reduced mortality.

Background

Patients with co-morbidities are particularly vulnerable to severe COVID-19 disease, with the UK's RECOVERY trial reporting diabetes in 27% of patients, heart disease in 26%, and chronic lung disease in 22%, with 57% having at least one major co-morbidity (1). Patients with COVID-19 can progress to a hyper-inflammatory state characterized by hypotension and tachycardia with high inflammatory markers (C-reactive protein (CRP), procalcitonin and ferritin) often requiring organ support in a critical care unit (ICU).

The avoidance of tachycardia is important in patients with cardiovascular disease. It is well established that a raised heart rate on admission to hospital for acute myocardial infarction is an independent predictor of mortality (2–4). A recent review suggested that discharge heart rates below 80 were also protective in hospitalized patients following myocardial infarction (5) and, importantly, with those with

hypertension (6) and that this protection was noted at longer-term follow up (7). Although it is unknown whether this protection extends to patients infected with COVID-19, some clinicians prescribe beta blockers to mitigate potential occult ischemic heart disease and to protect patients following reports of COVID-induced myocarditis and cardiomyopathy (8, 9).

Although developed for cardiovascular protection (10, 11), a growing body of evidence suggests that patients may benefit from beta-blockade through immunomodulation. The majority of lymphoid cells express beta-adrenergic receptors on their surface after acute activation (12). Acute autonomic dysfunction and tachycardia are associated with a poor outcome in hyper-inflammatory states such bacterial septic shock (13) with mortalities over 70% (14). Beta blockade has also been associated with improved outcomes in a variety of conditions including septic shock (15), myocarditis (16), liver failure (17), multiple myeloma (18), traumatic brain injury (19), trauma (20) and burns (21).

Physicians in our institution (an NHS hospital with one of the largest cohorts of COVID-19 patients in the UK) used individual judgement to prescribe beta-blockade to control persistent tachycardia in critically ill COVID-19 patients. During otherwise highly protocolized treatment of COVID-19, beta-blockade was one of the few aspects of patient management left to individual clinical discretion. Overall, our clinicians who direct care on the ICU were in equipoise about the utility of beta-blockade to affect the outcome of COVID-19 disease, a necessary precondition for leading the STRESS-L study (STudy into the REversal of Septic Shock with Landiolol (Beta Blockade)) (22).

Methods

Setting

This audit was undertaken at University Hospitals Birmingham NHS Foundation Trust (UHB), which serves an ethnically diverse population of approximately 1.5 million people and to which 1671 patients with Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) proven COVID-19 disease were admitted during the timespan of the audit. This was a single-institution audit which was registered and approved by the UHB Clinical Audit Registration & Management System (Reference: CARMS-16024), and which did not require separate ethical approval.

Population

In the absence of prior data on beta-blocker use in COVID, we used all available patient data without a prior power calculation, based on all hospital admissions between mid-February and mid-November 2020 which included the peak period (March to May) of the pandemic locally. We studied all patients where COVID-19 was PCR-confirmed from nasopharyngeal, sputum or bronchoalveolar samples.

During this phase of the pandemic, patients admitted to our hospital were treated with oxygen, self-proning and thromboprophylaxis (enoxaparin 1 mg/kg/day) as standard general ward care. Antibiotics were administered to patients with known or suspected bacterial infection. At the time of data collection,

our Institution recruited to RECOVERY (23) and REMAP-CAP (24) platform trials which were open-labelled studies. We identified all prescription data for steroids (25). Those patients who met the criteria of a respiratory rate of 30 or more breaths per minute, and inspired oxygen fractions (FiO2) at 0.6 or more to maintain oxygen saturations (SpO2) of 92% and with an Oxford Clinical Frailty Score (CFS) (26) of 4 or less were admitted to the ICU for invasive mechanical ventilation. Once the decision to admit to ICU had been made, patients were intubated and ventilated according to a pre-defined protocol. We selected this period of audit as ICU management was consistent during this phase of the pandemic. Our institution did not use non-invasive respiratory support during this period of intense COVID surge. ICU care was protocolized as far as possible.

The use of beta-blockade was at the decision of the consultant (attending) covering each twelve-hour shift which meant that there were no fixed criteria for beta blocker initiation nor by how much the heart rate should be reduced. The senior clinicians were in equipoise around the utility of beta blockade and were free to stop existing prescriptions. We were aware that observational retrospective data analysis presents the risk of immortal time bias as participants must have survived to receive the intervention (27). We therefore created a 28-day Cohort Trial (28, 29) whose entry criteria (based on the STRESS-L study) (22) were to be receiving treatment with norepinephrine and to have a heart rate (HR) of 90 beats per minute (bpm) for more than 12 hours.. We recorded time from entry criteria to the first dose of beta blocker. Patients who received beta blockade before ICU admission were excluded. As the trial was censored at 28 days, those patients who did not receive a beta blocker were allocated a nominal time to beta blocker treatment of 29 days, beyond the censor point for the purposes of the analysis. Patients who were discharged from hospital by day 28 were assumed to have survived beyond the 28-day censor.

Data extraction

The variables extracted from the electronic medical records were demographic data: sex, age, ethnicity (White, Black, Asian, Minority Ethnic), dates of admission and discharge to hospital, dates of admission and discharge to ICU, status at ICU and hospital discharge (dead/alive). Clinical data included: beta-blockade (type, time of dose), heart rate (bpm) and Entry criteria and at discharge from hospital or day 28 whichever was later, APACHE II score (30), steroid use (type, dose) and admission laboratory results (CRP (mg/L), Neutrophil (10^9/L), Lymphocyte (10^9/L), Neutrophil:Lymphocyte ratio). For ease of interpretation and because patient numbers were relatively small, ethnicity was classified as a binary status (“white” or “non-white”). Steroid use varied in type (dexamethasone, prednisolone, methyl prednisolone) and dose, so steroid use was classified as steroid status (“Yes” or “No”).

Exposure of interest

The main exposure of interest was treatment with beta-blockade.

Outcomes

The primary outcome of interest was death within 28 days of entry into the Cohort Trial. Secondary outcomes included overall survival in-hospital, length of stay on ICU and changes in white cell count and

CRP.

Statistical analysis

Descriptive statistics of patient characteristics and outcomes were compared between the beta-blockade and no beta-blockade groups to identify potential confounders. Continuous outcomes were summarized using mean and standard deviation (SD) and compared using a two-sample t-test. Categorical data were compared using frequency and percentage and compared using the chi-square test or Fisher's exact test. Any non-normal data were summarized using the median and inter-quartile range (IQR) and compared using the Wilcoxon rank-sum test. The starting norepinephrine dose used in the adjusted mortality was normalized by log(e) transformation.

For the primary outcome of interest, data were analyzed using Cox Regression with Time Dependent Covariate Analysis to estimate the changes in mortality associated with increasing delay to first dose beta-blockade. All analyses were adjusted for potential confounders - age, gender, ethnicity, APACHE II score, steroid status and log-transformed norepinephrine dose at Cohort Trial start. Data results were presented using adjusted hazards ratio.

Secondary outcomes were analyzed using linear regression (continuous dependent variable) and logistic regression (binary dependent variable). The secondary analyses were adjusted for the same variables as the primary analyses. The adjusted effect estimate and 95% CI are presented for all analyses. As use of beta blockade was not protocolized and some patients only received a few days' treatment, we performed an adjusted mortality analysis using similar covariates but adding the duration of treatment with beta blockers.

All statistical tests were two-sided and statistical significance was assessed at the 5% level. Analyses were conducted using IBM SPSS 26 (IBM, Armonk, NY).

Results

We extracted data for 276 patients who were admitted to the ICU with COVID-19 who were positive or became swab positive during their admission (Consort diagram, Fig. 1). Of these, five (1.8%) died within 6 hours of ICU admission and would not have been considered for beta blockade. A further 14 (5.1%) never reached the entry criterion of a heart rate greater than 90 bpm for 12 hours, while a further 22 (8.0%) were excluded because they were receiving beta blockers before admission to ICU. This left a cohort of 235 (85.1%) patients, 144 of whom received norepinephrine and were included in the analysis.

The characteristics of patients are summarized in Table 1. Average age was 56.1 years (SD 13.9), 102 (70.8%) were male, 54 (37.5%) were of white ethnicity and 90 (62.5%) were of non-white ethnicity. Patients had a mean APACHE II score of 14.3 (SD 4.0), a mean heart rate of 99.3 (SD 13.1) and mean CRP 183 (IRQ 111, 267). The predominance of males is consistent with national UK data (31). Males were also more likely to receive beta blocker treatment and this precluded a matched analysis. The only

significant difference was a lower final lymphocyte count in patients receiving beta blockade (1.2 vs 1.6 $x10^{-9}$/ml, p = 0.042).

Table 1
Baseline demographic and clinical characteristics summarized by beta blockade status

Criteria	No Beta Blockade (N = 61)	Beta Blockade (N = 83)	Overall (N = 144)	P-value
Age (years), Mean (SD)	57.1 (12.8)	55.3 (12.5)	56.1 (13.9)	0.399
Gender (male), N (%)	35 (57.4)	67 (80.7)	102 (70.8)	0.002
Ethnicity, N (%)				
White	23 (37.7)	31 (37.4)	54 (37.5)	0.965
Non-white	38 (62.3)	52 (62.6)	90 (62.5)	
Steroid use (Yes), N (%)	32 (52.5)	46 (55.4)	78 (54.2)	0.724
Apache II, Mean (SD)	14.3 (4.4)	14.3 (4.0)	14.3 (4.0)	0.970
Time from ICU Admission to Heart Rate > = 90 Median (IQR) Days				
	0.58 (0.18, 1.48)	0.38 (0.16, 1.23)	0.50 (0.17, 1.32)	0.422
Norepinephrine Dose Median (IQR) mcg/kg/min				
Start*	0.06 (0.03, 0.10)	0.07 (0.03, 1.04)	0.07 (0.03, 0.10)	0.547
Heart Rate Mean (SD) bpm				
Start	99.2 (13.1)	99.4 (13.3)	99.3 (13.1)	0.904
End	95.8 (22.7)	94.0 (18.1)	94.8 (20.1)	0.593
C-Reactive Protein Median (IQR) mg/L				
Start	194 (141, 280)	173 (101, 252)	183 (111, 267)	0.200
End	97 (18, 215)	61 (14, 174)	63 (16, 197)	0.167

IQR: 25% and 75%

* All alive patients had been weaned from Norepinephrine at 28-days

Criteria	No Beta Blockade (N = 61)	Beta Blockade (N = 83)	Overall (N = 144)	P-value
Lymphocyte Count Median (IQR) x 10^{-9} /ml				
Start	1.0 (0.6, 1.3)	1.0 (0.7, 1.5)	1.0 (0.6, 1.4)	0.382
End	1.2 (0.9, 1.9)	1.6 (1.1, 2.2)	1.4 (1.0, 2.1)	0.042
Neutrophil Count Median (IQR) x 10^{-9} /ml				
Start	8.8 (6.7, 12.0)	8.3 (5.9, 13.1)	8.45 (6.3, 12.4)	0.805
End	9.4 (6.3, 13.9)	8.1 (5.7, 14.5)	8.8 (5.9, 14.3)	0.522
Neutrophil:Lymphocyte Ratio Median (IQR)				
Start	8.27 (6.36, 13.45)	8.30 (5.58, 15.23)	8.28 (5.85 13.71)	0.528
End	7.84 (3.95, 13.94)	4.77 (3.18, 12.33)	6.01 (3.33, 12.94)	0.079
IQR: 25% and 75%				
* All alive patients had been weaned from Norepinephrine at 28-days				

For the beta blocker group, the mean time from entry criteria to starting beta blockers was 7.91 days (IQR 3.89, 13.15) (Table 2). The median length of treatment was seven days with 25% of patients receiving fewer than four days treatment (IQR 4.0–14.0). Beta blockers were used for 396 days (17.4%) out of a possible follow up period of 28 days in 83 patients (Total possible 2324 days) and only 46 of the 83 (55.4%) patients demonstrated a reduction in heart rate of 10% or more of baseline in the 24 hours following initiation.

Table 2
Beta Blocker Compliance with Therapy

Time from Cohort Trial Entry to Beta Blocker Median (IQR) Days	**7.91 (3.89, 13.15)**
Duration of Beta Blocker Therapy Median (IQR) Days	7.0 (4.0, 14.0)
Number of Beta Blocker Treated patients with 10% decrease of Heart Rate at 24 hours	46/83 (55.4%)

Of the 83 beta blocker patients, 24 (28.9%) died within 28 days compared with 47.5% of those not treated with beta blockers. From the adjusted primary analyses, there was a statistically significant association with beta blocker treatment and 28-day mortality (adjusted odds ratio 0.43 95% (CI 0.20–0.95) p = 0.036) (Table 3 and Fig. 2). To compensate for the risk of immortal time bias, we performed Cox regression with time-dependent covariate analysis. This suggested that delay in exposure to beta blockade was associated with an increased risk of death, though this did not achieve statistical significance (Hazard Ratio 1.42 p = 0.264). Exposure to beta blockade was associated with an adjusted odds ratio for death of 0.76 (95% CI 0.64–0.91; P = 0.002) for each day treated with beta blockade.

Table 3
Mortality data summarised by beta blockade status

Analysis	No Beta Blockade (N = 61)	Beta Blockade (N = 83)	
Cox Regression Analysis Died in ICU within 28 days N (%)	29/61 (47.5%)	24/83 (28.9%)	**Adjusted OR (95% CI); P-value**: 0.43 (0.20, 0.95); P = 0.036
Cox Regression with Time Dependent Analysis Died in ICU within 28 days N (%)			**Exp(B); P-value**: 1.42; P = 0.264
Logistic Regression of Beta Blocker Exposure No of Days out of total possible (%)		396/2324 (17.4%)	**Adjusted OR (95% CI); P-value**: 0.76 (0.64, 0.91); P = 0.002
Length of ICU stay (days), median (IQR)	13.7 (6.6, 21.4)	23.8 (15.8, 33.1)	< 0.001
Length of Hospital stay (days), median (IQR)	19.8 (10.1, 34.2)	34.2 (22.8, 47.5)	< 0.001
Adjusted for the variables Age, Gender, APACHE-II, Ethnic Status, Steroid use and Log Transformed Norepinephrine Dose at Trial Start			
In both Cox Regression analyses, Gender and Log Transformed Norepinephrine Dose were significant at P < 0.05			

For the secondary outcomes (Table 3), there was a statistically significant difference in the median lengths of ICU stay (beta blockade group 23.8 days (IQR 15.8, 33.1), no beta-blockade group 13.7 days (IQR 6.6, 21.4) ($p < 0.001$), and hospital stay 34.2 days (IQR 22.8, 47.5) versus 19.8 days (IQR 10.1, 34.2) ($p < 0.001$) respectively.

Discussion

We report an association between treatment with beta-blockade and lower 28-day mortality in critically ill COVID-19 patients with tachycardia requiring norepinephrine to support blood pressure. Some of this effect is attributable to immortal time bias (27): the difference was no longer statistically significant following Cox regression with time dependent covariate analysis. Our Cohort Trial was similar to the prospective trial STRESS-L (22) currently under way for septic shock in the UK to test the hypotheses that beta blockade is protective from adverse effects of catecholamine exposure. Autonomic dysfunction and tachycardia are associated with a poor outcome in septic shock (13, 14), and may be driven by the use of norepinephrine: bradycardia is protective (32). Tachycardia is associated with increased mortality in ICU

COVID-19 (33). We hypothesize that in severe COVID-19, IL-6-mediated systemic inflammation (34–36) is further aggravated by β2-adrenergic stimulation, while beta-blockade may counteract this effect by protecting the synthesis of anti-inflammatory cytokines (for example, IL-10) (37–39).

We protocolized the management of our critically ill Covid patients in almost all respects except use of beta-blockade and management of heart rate targets which reflects clinician equipoise for the STRESS-L study participation. Most patients (88.2%) received bisoprolol and so we were unable to perform an analysis to distinguish whether more benefit was derived from cardioselective agents. We attempted a matched analysis but were unable to match the groups in large enough numbers to be meaningful. As these patients were all treated with norepinephrine, use of beta blockade was delayed and low. It may be that more aggressive dosing would have had a detectible effect. Treatment with beta blockade was also associated with longer ICU stay; it is conceivable that the use of beta-blockade may have enabled survival (with a prolonged ICU stay) of patients who would otherwise have died earlier.

Given a signal for benefit, and the absence of evidence of harm, we would propose that critically ill Covid-19 patients should be included in current randomized controlled trials of beta-blockade in sepsis.

Conclusions

In a Cox Regression with Time Dependent Covariate of retrospective data, delay of introduction of beta blockade was associated with an increased but non-significant mortality but was accompanied by an increase in ICU stay during management of critically ill COVID-19 patients with severe COVID-19 disease. A prospective study of heart rate control with beta-blockade to improve outcomes in COVID-19 disease is recommended.

Declarations

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE: This was a single-institution audit which was registered and approved by the UHB Clinical Audit Registration & Management System (Reference: CARMS-16024), and which did not require separate ethical approval.

CONSENT FOR PUBLICATION: All authors consent to publication

AVAILABILITY OF SUPPORTING DATA: Support Data will be available upon formal request

COMPETING INTERESTS: Prof Whitehouse is the Chief Investigator for the NIHR EME funded STRESS-L Study (Project Number - 14/150/85, ISRCTN12600919, EudraCT: 2017-001785-14), Prof Bion is a co-applicant for STRESS-L, Prof Lall is the Clinical Trialist for STRESS-L, Dr Hossain and Dr Mistry are the Data Analysts for STRESS-L

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References

1. Recovery Collaborative Group. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;383(21):2030–40.
2. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KAA, Yusuf S. Adverse Impact of Bleeding on Prognosis in Patients With Acute Coronary Syndromes. Circulation. 2006;114(8):774–82.
3. Madsen EB, Gilpin E, Henning H, Ahnve S, LeWinter M, Ceretto W, et al. Prediction of late mortality after myocardial infarction from variables measured at different times during hospitalization. The American Journal of Cardiology. 1984;53(1):47–54.
4. Hjalmarson A, Gilpin EA, Kjekshus J, Schieman G, Nicod P, Henning H, et al. Influence of heart rate on mortality after acute myocardial infarction. Am J Cardiol. 1990;65(9):547–53.
5. Alapati V, Tang F, Charlap E, Chan PS, Heidenreich PA, Jones PG, et al. Discharge Heart Rate After Hospitalization for Myocardial Infarction and Long-Term Mortality in 2 US Registries. J Am Heart Assoc. 2019;8(3):e010855.
6. Dalal J, Dasbiswas A, Sathyamurthy I, Maddury SR, Kerkar P, Bansal S, et al. Heart Rate in Hypertension: Review and Expert Opinion. Int J Hypertens. 2019;2019:2087064.
7. Jensen MT, Kaiser C, Sandsten KE, Alber H, Wanitschek M, Iversen A, et al. Heart rate at discharge and long-term prognosis following percutaneous coronary intervention in stable and acute coronary syndromes–results from the BASKET PROVE trial. Int J Cardiol. 2013;168(4):3802–6.
8. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection. 2020;48(5):773–7.
9. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):819–24.
10. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2017;1:CD002003.
11. Safi S, Sethi NJ, Nielsen EE, Feinberg J, Jakobsen JC, Gluud C. Beta-blockers for suspected or diagnosed acute myocardial infarction. Cochrane Database Syst Rev. 2019;12:CD012484.

12. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve–an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000;52(4):595–638.
13. Schwartz A, Brotfain E, Koyfman L, Klein M. Cardiac Arrhythmias in a Septic ICU Population: A Review. J Crit Care Med (Targu Mures). 2015;1(4):140–6.
14. Schmidt H, Muller-Werdan U, Hoffmann T, Francis DP, Piepoli MF, Rauchhaus M, et al. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. Crit Care Med. 2005;33(9):1994–2002.
15. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA. 2013;310(16):1683–91.
16. Wang JF, Meissner A, Malek S, Chen Y, Ke Q, Zhang J, et al. Propranolol ameliorates and epinephrine exacerbates progression of acute and chronic viral myocarditis. Am J Physiol Heart Circ Physiol. 2005;289(4):H1577-83.
17. Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, et al. Non-selective beta-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut. 2015;64(7):1111–9.
18. Hwa YL, Shi Q, Kumar SK, Lacy MQ, Gertz MA, Kapoor P, et al. Beta-blockers improve survival outcomes in patients with multiple myeloma: a retrospective evaluation. Am J Hematol. 2017;92(1):50–5.
19. Cotton BA, Snodgrass KB, Fleming SB, Carpenter RO, Kemp CD, Arbogast PG, et al. Beta-blocker exposure is associated with improved survival after severe traumatic brain injury. J Trauma. 2007;62(1):26–33.
20. Arbabi S, Campion EM, Hemmila MR, Barker M, Dimo M, Ahrns KS, et al. Beta-blocker use is associated with improved outcomes in adult trauma patients. J Trauma. 2007;62(1):56–61.
21. Arbabi S, Ahrns KS, Wahl WL, Hemmila MR, Wang SC, Brandt MM, et al. Beta-blocker use is associated with improved outcomes in adult burn patients. J Trauma. 2004;56(2):265-9; discussion 9–71.
22. Lall R, Mistry D, Skilton E, Boota N, Regan S, Bion J, et al. Study into the reversal of septic shock with landiolol (beta blockade): STRESS-L Study protocol for a randomised trial. BMJ Open. 2021;11(2):e043194.
23. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020.
24. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. Ann Am Thorac Soc. 2020;17(7):879–91.
25. Dexamethasone in. Hospitalized Patients with Covid-19 — Preliminary Report. New England Journal of Medicine; 2020.

26. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95.
27. Yadav K, Lewis RJ. Immortal Time Bias in Observational Studies. JAMA. 2021;325(7):686–7.
28. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758–64.
29. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period—application to control of the healthy worker survivor effect. Mathematical Modelling. 1986;7(9):1393–512.
30. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
31. Intensive Care National Audit and Research Centre. COVID-19 reporting from the Case Mix Programme 2021 [Available from: https://www.icnarc.org/our-audit/audits/cmp/reports.
32. Beesley SJ, Wilson EL, Lanspa MJ, Grissom CK, Shahul S, Talmor D, et al. Relative Bradycardia in Patients With Septic Shock Requiring Vasopressor Therapy. Crit Care Med. 2017;45(2):225–33.
33. Ferrando-Vivas P, Doidge J, Thomas K, Gould DW, Mouncey P, Shankar-Hari M, et al. Prognostic Factors for 30-Day Mortality in Critically Ill Patients With Coronavirus Disease 2019: An Observational Cohort Study. Critical care medicine. 2021;49(1):102–11.
34. Zhou Y, Fu B, Zheng X, Wang D, Zhao C, qi Y, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. Natl Sci Rev. 2020:nwaa041.
35. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2021;397(10285):1637–45.
36. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491–502.
37. Muthu K, Deng J, Gamelli R, Shankar R, Jones SB. Adrenergic modulation of cytokine release in bone marrow progenitor-derived macrophage following polymicrobial sepsis. J Neuroimmunol. 2005;158(1–2):50–7.
38. Deng J, Muthu K, Gamelli R, Shankar R, Jones SB. Adrenergic modulation of splenic macrophage cytokine release in polymicrobial sepsis. Am J Physiol Cell Physiol. 2004;287(3):C730-C6.
39. Severn A, Rapson NT, Hunter CA, Liew FY. Regulation of tumor necrosis factor production by adrenaline and beta-adrenergic agonists. J Immunol. 1992;148(11):3441–5.

Figures

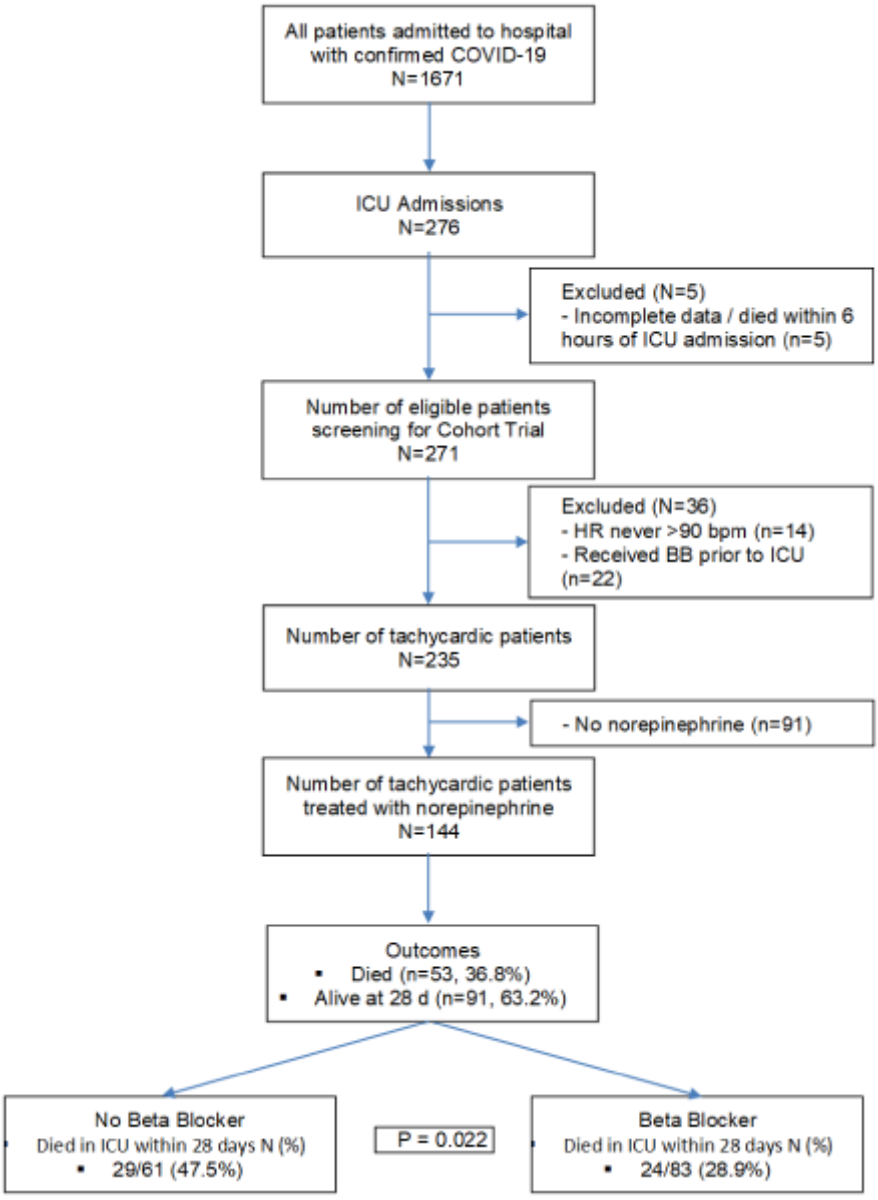

Figure 1

CONSORT Diagram for Audit Population

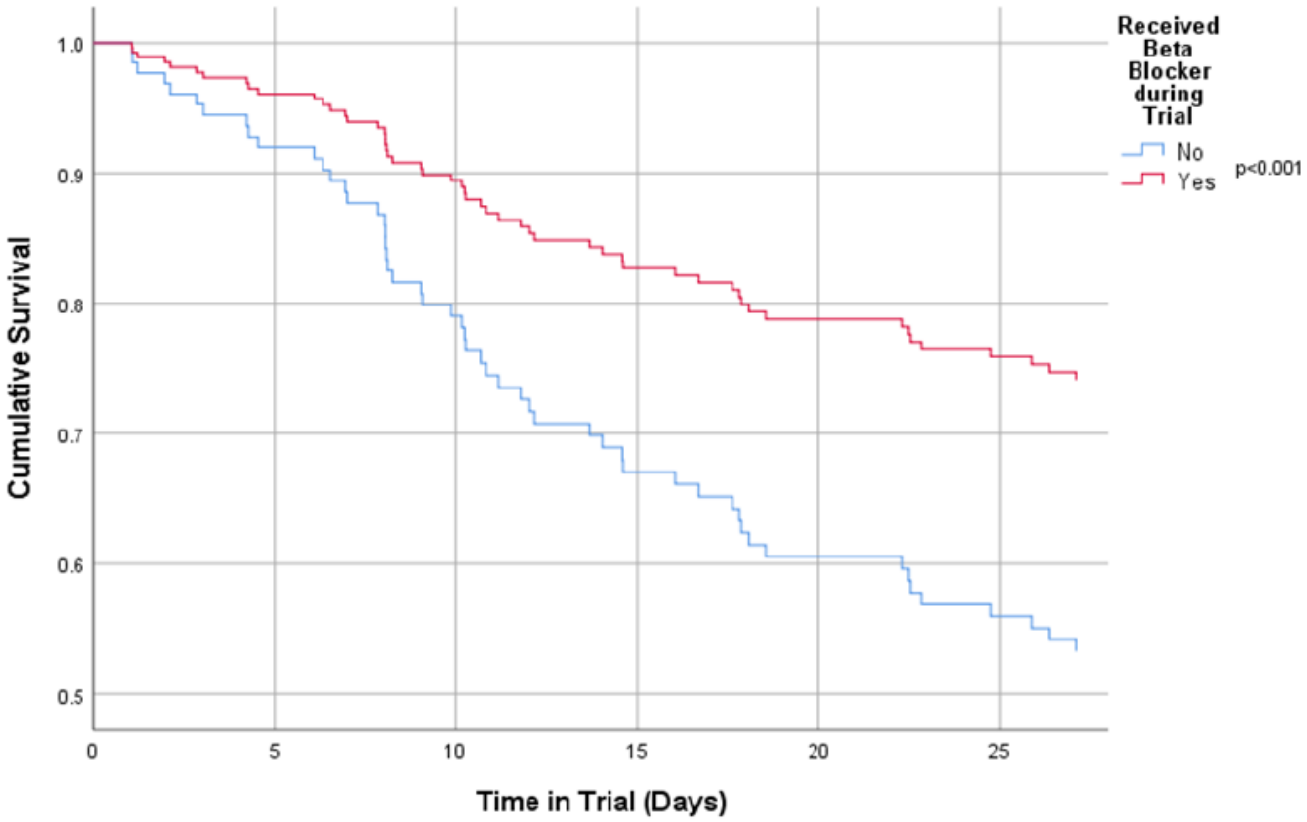

Figure 2

Cox Regression Analysis adjusted by Age, Gender, APACHE-II, Ethnic Status, Steroid use and Log Transformed Norepinephrine Dose at Trial Start with High Risk of Immortal Time Bias