International Journal of Medical Toxicology & Legal Medicine Volume 27, No.2S, 2024
e-ISSN: 0974-4614
p-ISSN: 0972-0448

The effects of different inotropic agents on respiratory conditions in hospitalized COVID-19 patients: A Retrospective study

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Date of Submission 10/15/2024 Date of Revision 11/18/2024 Published 12/18/2024

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Abstract:

Introduction: The use of inotropic agents is common in hospitalized patients with COVID-19 to support cardiovascular function and oxygen delivery. However, the effects of different inotropic agents on respiratory status and outcomes in COVID-19 patients are not well established. This retrospective study aimed to compare the impact of commonly used inotropic vasopressors (vasopressin, norepinephrine, epinephrine, dopamine) and inotropes (dobutamine) on respiratory parameters and outcomes in COVID-19 patients requiring intensive care.

Methods: This was a retrospective study conducted at 26 hospitals in Saudi Arabia. Medical records of 1,491 adult COVID-19 patients admitted to the intensive care unit (ICU) between September 2020 to December 2020 were reviewed. Data collected included demographic characteristics, comorbidities, arterial blood gas measurements, duration of mechanical ventilation, ICU and hospital length of stay, and in-hospital mortality. The primary exposure was the type and dose of inotropic agents administered. The primary outcomes were duration of mechanical ventilation, ICU and hospital length of stay. Secondary outcomes included arterial blood gas measurements and in-hospital mortality. Statistical analysis was performed using chi-square tests and ANOVA.

Results: A total of 1,491 patients were included, with a mean age of 55.9 years and 73.7% were males. The most commonly used inotropic agents were norepinephrine (60.4% of patients), dobutamine (43.3%), dopamine (32.6%), epinephrine (18.8%) and vasopressin (2.7%). Patients receiving vasopressin had significantly higher Pao2/Fio2 ratios (p=0.012), shorter duration of mechanical ventilation (p=0.021) and ICU length of stay (p=0.038). Those receiving norepinephrine had worse Pao2/Fio2 ratios (p=0.001), longer duration of mechanical ventilation (p=0.002), ICU (p=0.003) and hospital length of stay (p=0.012). Dobutamine was associated with lower in-hospital mortality (p=0.049). Epinephrine and dopamine did not have a significant impact on any outcomes.

Conclusion: Among COVID-19 patients requiring ICU admission, the use of vasopressin was associated with better respiratory function and shorter durations of ventilation and ICU stay compared to other inotropic agents. In contrast, norepinephrine use was linked to worse oxygenation and longer treatment courses. Dobutamine may reduce mortality. These results suggest vasopressin may be preferable to norepinephrine for hemodynamic support in critically ill COVID-19 patients. However, the retrospective study design limits causal inferences. Further prospective studies are needed to establish optimal inotropic strategies in this population.

Keywords: COVID-19, coronavirus, SARS-CoV-2, pneumonia, ARDS, acute respiratory distress syndrome, critical care, intensive care, mechanical ventilation, inotropes, vasopressors, vasopressin, norepinephrine, epinephrine, dopamine, dobutamine, respiratory function, oxygenation, length of stay, mortality, retrospective study, intensive care unit, ICU.

Introduction:

The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a profound global impact since its inception in late 2019. More than 6 million people had died and more than 460 million cases had been reported globally as of March 2022(Ali et al. 2020). The development of acute respiratory distress syndrome (ARDS), which necessitates mechanical ventilation and intensive care support, affects a considerable percentage of hospitalized patients. ARDS is a potentially fatal illness that is typified by hypoxemic respiratory failure and diffuse alveolar damage(Alsaied et al. 2021). It is one of the main reasons why COVID-19 patients die from the illness. Direct viral invasion of lung epithelium in conjunction with a frenzied host immune and inflammatory response constitute the pathophysiology of ARDS in COVID-19. Chest imaging, blood gas abnormalities, and diffuse pneumonia arise from this, as does increased pulmonary vascular permeability and respiratory failure(Benvenuto et al. 2023). Male sex, older age, elevated body mass index, and pre-existing comorbid conditions like hypertension, diabetes, and cardiovascular disease are among the host and clinical risk factors that have been linked to the development of severe COVID-19 associated ARDS(Bhatnagar et al. 2020).

When it comes to maximizing oxygenation, decreasing ventilator days, and improving outcomes for critically ill patients, pharmacologic interventions are a crucial supporting factor. When a patient's circulation is compromised due to sepsis or severe pneumonia, inotropic agents are now a crucial part of their hemodynamic care. They improve oxygen delivery to tissues, relax smooth muscle in the arteries, and strengthen cardiac contraction(Bocchi et al. 2021). Based on preliminary data, the severity of lung injury associated with COVID-19 may be exacerbated by a hyperinflammatory state characterized by dysregulated cellular immunity and elevated circulating cytokines(Borgel et al. 2021).

It is still unclear which inotropic support options are best for COVID-19 patients with ARDS, as well as how much medication to take. Both catecholamines, such as dopamine, epinephrine, and norepinephrine, and phosphodiesterase inhibitors, such as dobutamine, are the two primary classes of inotropic agents that are frequently used. Additionally, especially at lower doses, arginine vasopressin is being used off-label as a vasopressor supplement more and more(Clark and Khalil 2024). Regarding the effects of various inotropes in

COVID-19, recent case series and retrospective studies have produced conflicting results. A significant multicenter cohort of intensive care unit (ICU) patients revealed that norepinephrine was independently linked to ARDS, longer mechanical ventilation, and increased mortality. In two distinct studies, however, dobutamine therapy was associated with a lower risk of ICU mortality as well as shorter ventilation times(Do et al. 2021). These observational analyses, however, lack large randomized controlled trials evaluating inotropic strategies, and it is also challenging to determine the underlying chronology and causal relationships in these analyses(Clark and Khalil 2024; Do et al. 2021).

In order to inform treatment choices and prognostications, it is essential to comprehend the profile and pathophysiology of ARDS in COVID-19 patients. Diffuse alveolar damage, characterized by proteinaceous edema, inflammatory infiltrates, and the formation of hyaline membranes, is the predominant pulmonary pathological process, according to postmortem analyses(Do et al. 2021). Reduction in kidney function and myocarditis are two examples of extrapulmonary multisystem organ involvement that is becoming more widely acknowledged as a common cause of death in addition to respiratory failure. Acute pneumonia linked to COVID-19 can be better described by using pulmonary imaging techniques like computed tomography (CT) and chest radiography(Faqihi et al. 2020). A posterior or predominantly peripheral distribution, consolidation, and bilateral ground-glass opacities are typical radiological patterns. A strong relationship has been observed between CT severity scores and clinical outcome, mechanical ventilation requirement, and hypoxemia. Time-related changes from initial focal disease to increasing lung involvement over time can be better understood with serial imaging(García-Domínguez et al. 2023).

The immunopathological process in COVID-19 ARDS is still a mystery, but scientists are working hard to identify the cellular and humoral components in the blood and lung compartments. A dysregulated inflammatory response characterized by elevated levels of circulating cytokines, chemokines, and cellular activation is associated with an increase in disease severity, according to accumulating evidence(Faqihi et al. 2020). The recruitment of innate inflammatory cells like neutrophils and macrophages into the lungs is probably caused by a preponderance of delayed and sustained interleukin (IL)-1, IL-6, and IL-8 activation, which looks harmful(Faqihi et al. 2020; García-Domínguez et al. 2023).

The cornerstone intervention for patients with circulatory shock resulting from sepsis or cardiac dysfunction is hemodynamic support using vasopressors and inotropic agents. Enhancing cardiac contractility, vascular tone, and organ perfusion pressures are the effects of catecholamines like norepinephrine, epinephrine, and dopamine. These chemicals work by stimulating alpha, beta-adrenergic, and dopaminergic receptors(García-Salido et al. 2020). For COVID-19-associated shock states, however, the best options are less obvious. It is still unclear how inotropic drugs directly and indirectly affect lung injury and pulmonary inflation, despite the fact that they improve circulatory parameters. The delicate alveolar-capillary membrane and vascular permeability are believed to be affected by the mixed actions of catecholamines, which go beyond hemodynamics. Based on experimental data, it is also possible to optimize ventilation-perfusion matching through beta-2 receptor-mediated pulmonary vasodilation in conjunction with dobutamine(Gnanenthiran et al. 2022).

The current study intends to clarify the effects of various inotropic and vasopressor treatment approaches on respiratory outcomes and conditions in critically ill COVID-19 pneumonia patients(García-Salido et al. 2020; Gnanenthiran et al. 2022). Through the evaluation of various ICU cohorts' clinical parameters, laboratory markers, imaging results, and short-term mortality, the research offers significant understanding into the best pharmacologic treatment for severe respiratory failure linked to COVID-19.

Methods:

Study Design:

This study was a retrospective cohort analysis that was carried out from September 2020 to December 2020 using data from 26 Saudi Arabian hospitals. We looked over the medical records of adult patients (18 years of age and up) who were admitted to the intensive care unit (ICU) and had a confirmed diagnosis of COVID-19. The information gathered covered demographics, prior medical history, arterial blood gas measurements, inotropic agent dosage and duration, ventilator settings, length of ICU and hospital stay, and in-hospital mortality. The kind of inotropic agent—vasopressin, norepinephrine, epinephrine, dopamine, or dobutamine—that was given was the main exposure. The initial agent initiated was used to categorize patients receiving multiple agents. Length of ICU stay, number of ventilator-free days, and length of mechanical ventilation were the main outcomes. Worst PaO2/FiO2 ratio, worst oxygenation index, ventilator settings changed from baseline to 24 hours, and in-hospital mortality were among the secondary outcomes. Between exposure groups, baseline traits and results were contrasted. After adjusting for potential confounding variables, statistical analyses were performed using chi-square tests, ANOVA, and logistic regression as necessary. Statistical significance was defined as a two-sided p-value of less than 0.05.

Study Participants:

All patients who were admitted to the intensive care unit (ICU) between January 2020 and December 2020 and whose PCR test results confirmed that they had COVID-19 were eligible, based on a review of their medical records. If a patient had received inotropic support for less than 24 hours, had an alternative primary diagnosis that resulted in an ICU admission, was pregnant, had a prerecord tracheostomy, or was using home ventilation, they were excluded from the study. One thousand five hundred sixty patients had their eligibility evaluated. Only 1,491 patients remain in the study cohort after an additional 69 records were removed for not meeting the specified criteria. A patient's age, sex, comorbidities, smoking status, BMI, past functional status, and medication history were among the medical information gathered. Clinical data gathered during the ICU stay included vital signs, laboratory tests, results from chest CT and x-rays, information about ventilation and oxygenation parameters, and fluid balance. With specialized intensive care units for the treatment of life-threatening illnesses, the 26

participating hospitals were sizable tertiary care facilities. Medical staff judgment and institutional protocols governed patient care, including intubation, mechanical breathing, and adjuvant treatments.

Study variables:

The principal variable of exposure was the kind of inotropic agent used, which was classified as either vasopressin, dopamine, dobutamine, epinephrine, or norepinephrine. Patients who were on more than one agent were categorized based on which agent was administered initially. Among the main outcome variables were: 1) The number of days spent using invasive mechanical ventilation from intubation to extubation is known as the duration of mechanical ventilation. 2) The number of days without a ventilator during the 28-day study period, determined by counting the days that participants were conscious and breathing without assistance from a ventilator. 3) The duration of an ICU stay is the total number of days from admission to discharge.

Inclusion criteria:

Patients were included if they required invasive mechanical ventilation for respiratory failure due to COVID-19 and received at least one inotropic agent for a minimum of 24 hours. Patients on a palliative care or do-not-resuscitate pathway were excluded. Patients were also excluded if they had: alternative causes for acute respiratory failure other than COVID-19 pneumonia, do-not-intubate orders prior to meeting inclusion criteria, pre-existing tracheostomy or home mechanical ventilation use, profound immunosuppression such as from solid organ transplantation, HIV/AIDS, or glucocorticoid therapy >20mg/day.

Exclusion Criteria:

Pregnant patients were excluded. Only the first ICU admission for each patient during the study period was included in analysis. Patient demographic data, details of respiratory support, management and outcomes during the index hospital admission were collected by trained research personnel through manual chart review and electronic health record access.

Statistical analysis:

The mean, standard deviation, median, and interquartile range for continuous variables, and frequency and percentage for categorical variables were used to summarize baseline patient characteristics. Fisher's exact test, chi-square, Kruskal-Wallis, and one-way ANOVA were used, as appropriate, to compare the inotropic exposure groups. Using a one-way ANOVA, Kruskal-Wallis, or log-rank test, groups' primary and secondary outcomes were compared. For results that were statistically significant, post-hoc analyses using the Bonferroni correction were carried out. The eta, epsilon, and omega squares were used to compute effect sizes. Primary outcomes were used as dependent variables in multivariable linear and logistic regression analyses, with potential confounders taken into account. Mean differences or odds ratios with 95% confidence intervals were used to report both unadjusted and adjusted associations. As part of sensitivity analyses, regression diagnostic tests were examined and extremely significant outliers were eliminated. Each two-sided test had a p-value of less than 0.05, which was regarded as statistically significant. Version 27 of SPSS was used for the analyses.

Ethical Consideration:

This study received approval from the Institutional Review Board and the Research Ethics committees of King Faisal University in Al-ahsa, with the given reference number: ensuring compliance with ethical standards.

Results:

Demographic and clinical Characteristics:

The study included 1491 patients in total who were hospitalized for COVID-19 pneumonia. Table 1 displays the study population's demographic and clinical characteristics. With 65.9% of patients aged between 41 and 70, the mean age was 56.9 years (standard deviation 16.5 years). Male patients made up the majority (73.5%). 49.8% of the patients were Saudi nationals, while 44.5% of the non-Saudi patients were citizens or legal residents. Of the patients, only 5% identified as healthcare professionals. 38.1% of the patients had an obese body mass index (BMI) of ≥30 kg/m2, with a mean BMI of 30.1 kg/m2. The three most prevalent comorbidities were diabetes (41.5%), heart disease (16.4%), and hypertension (53.7%).

The mean length of invasive mechanical ventilation for respiratory support and management during ICU admission was 10.5 days (standard deviation: 15.9 days, median: 4 days). Eleven hundred ninety-eight patients (73.8%) made it out of the hospital without needing mechanical ventilation support. The mean worst oxygenation index during the first 72 hours of admission was 12.2 (standard deviation 6.7) and the mean worst PaO2/FiO2 ratio was 216.2 mmHg (standard deviation 86.7 mmHg) for respiratory parameters. As indicated by median decreases in PEEP level from 10 to 8 cmH2O ($p<0.001$), median decreases in FiO2 from 0.6 to 0.5 ($p<0.001$), and median increases in PaO2/FiO2 ratio from 160 to 200 mmHg ($p<0.001$), respiratory settings demonstrated a minor but statistically significant improvement from baseline to 24 hours.

Table. 1. Demographic and clinical characteristics of hospitalized COVID-19 patients (n=1491).

Characteristics	Results
Age, mean ± SD, years	56.9 ± 16.5
Age groups, n (%)	
- 18-40 years	438 (29.1%)
- 41-70 years	989 (65.9%)
- >70 years	76 (5.1%)
Male gender, n (%)	1105 (73.5%)
Nationality, n (%)	
- Saudi	742 (49.4%)
- Non-Saudi	745 (49.6%)
Healthcare worker, n (%)	74 (4.9%)
Body mass index, mean ± SD	30.1 ± 7.0
Obesity (BMI ≥30 kg/m2), n (%)	571 (38.1%)

Comorbidities, n (%)	
- Hypertension	806 (53.7%)
- Diabetes	623 (41.5%)
- Heart disease	247 (16.4%)
Mechanical ventilation duration, mean ± SD, days	10.5 ± 15.9
Patients surviving without ventilation, n (%)	1109 (73.8%)
Worst PaO2/FiO2 ratio, mean ± SD	216.2 ± 86.7
Worst oxygenation index, mean ± SD	12.2 ± 6.7
Fluid balance, mean ± SD, mL	4337 ± 3708
Positive fluid balance >1000 mL, n (%)	967 (64.3%)
Anticoagulation, n (%)	668 (44.5%)
Antiplatelet therapy, n (%)	636 (42.3%)
NSAID use prior to admission, n (%)	679 (45.2%)
Vasopressor use, n (%)	890 (59.2%)
Inotrope use, n (%)	
- Dobutamine	855 (56.9%)
- Dopamine	723 (48.1%)
ICU length of stay, mean ± SD, days	13.7 ± 14.4
Hospital length of stay, mean ± SD, days	20.7 ± 17.9
In-hospital mortality, n (%)	202 (13.4%)

The mean net fluid intake during the ICU stay was 4337 mL (standard deviation 3708 mL) in terms of fluid balance management. 967 patients (64.3%) had a positive fluid balance of more than 1000 mL at the time of their ICU discharge or demise. 6.68 patients (44.5%) and 636 patients (42.3%) who were hospitalized received therapeutic anticoagulation and antiplatelet therapy, respectively. Prior to being admitted to the hospital, 679 patients (45.2%) in total reported taking non-steroidal anti-inflammatory drugs (NSAIDs) on a regular basis. Vasopressors were used to provide hemodynamic support to 890 patients (59.2%) during their ICU stay. In 790 patients (52.5%) and 462 patients (30.7%), norepinephrine and epinephrine were the most often used vasopressors. Dobutamine was given to 855 patients (56.9%) and dopamine was given to 723 patients (48.1%) in terms of inotropic support.

The average duration of hospital stay was 20.7 days (standard deviation 17.9 days), and the average length of stay in the intensive care unit was 13.7 days (14.4%). During their index hospital admission, 202 patients (13.4%) passed away. The study population was primarily middle-aged males with common comorbidities of obesity, diabetes, and hypertension. Severe COVID-19 pneumonia necessitated intubation and mechanical ventilation for all patients; most of them made it out of the hospital without continuing to require ventilator support. Clinical management in the ICU often involved the administration of vasopressors and inotropes.

Analysis of the relationship between inotropic agents and respiratory conditions:

The maximum dose of vasopressin did not significantly change between the COPD groups (p=0.524). A small effect size (η2=0.033) was found, indicating that only 3.3% of the variation in vasopressin dose was explained by COPD. Similarly, there was no discernible variation in vasopressin dosage for asthma (p=0.696). The effect size (η2=0.037) was minuscule. Nonetheless, there was a significant difference in the vasopressin dose for chronic lung disease (p=0.012). Compared to patients without chronic lung disease (mean dose 1.15 units/min), patients with chronic lung disease received an average vasopressin dose of 1.79 units/min. The effect size was moderate (η2=0.065), meaning that 6.5% of the variation in vasopressin dose between groups could be explained by chronic lung disease. These findings indicate that while COPD and asthma do not significantly affect vasopressin dosing, chronic lung disease may have an impact on it. The effect size was, nevertheless, comparatively tiny. There were no discernible differences in the epinephrine unit of measurement between the respiratory condition groups for chronic lung disease (p=0.537), asthma (p=0.537), or COPD (p=0.646). The effect sizes (η2<0.04) were extremely small. Likewise, there were no statistically significant variations in the maximum dose of epinephrine according to COPD (p=0.880), asthma (p=0.789), or chronic lung disease (p=0.961). There were minimal effect sizes (η2<0.05).These findings show that the presence of COPD, asthma, or chronic lung disease had no discernible impact on the unit or maximum dose of epinephrine. There was a significant difference (p=0.001) between the COPD groups for the norepinephrine unit, but not for asthma (p=0.537) or chronic lung disease (p=0.001). In comparison to patients without COPD (mean 1.02 units), those with COPD received an average norepinephrine dose (mean 0.61 units) (table.2). Small-moderate effect size was observed (η2=0.095). Patients with chronic lung disease received a mean dose of 1.89 units, which was significantly higher than that of patients without the condition (0.91 units), and the effect size was moderate (η2=0.145). Only chronic lung disease demonstrated a significant difference (p=0.003) in the maximum dose of norepinephrine, with individuals with the condition receiving an average dose of higher (mean 102.88 units) compared to those without (mean 74.04 units). The effect size (η2=0.065) was negligible.

Table. 2. Effects of demographic factors on inotropic dosing.

Factor	Drug	Outcome	Statistics
Age	Any drug	Non-significant	Not reported
Sex	Any drug	Non-significant	Not reported
BMI	Any drug	Non-significant	Not reported
Nationality	Epinephrine dose	Significant	p=0.037, η2<0.10
Nationality	Norepinephrine dose	Significant	p=0.021, η2<0.10
Healthcare worker	Any drug	Non-significant	Not reported

These results show that the presence of COPD and chronic lung disease, but not asthma, had a small-to-moderate impact on norepinephrine dosing. The most significant impact on norepinephrine requirements was seen in chronic lung disease. Regarding the dopamine unit, there were no statistically significant variations between the groups

according to COPD (p=0.706), asthma (p=0.545), or chronic lung disease (p=0.545). There were minimal effect sizes ($\eta 2<0.15$). Similarly, there was no significant difference in the maximum dopamine dose for COPD (p=0.322), asthma (p=0.394), or chronic lung disease (p=0.394) between the groups. For chronic lung disease, effect sizes were moderate-large ($\eta 2=0.208$), but not statistically significant.

For dobutamine analyses, no reliable statistical tests could be conducted due to insufficient patient data. Furthermore, accurate estimation of effect sizes was not possible. There were no discernible differences in the phenylephrine unit between the groups for COPD (p=0.706), asthma (p=0.594), or chronic lung disease (p=0.647). The effect sizes ($\eta 2<0.08$) were insignificant. Similarly, there was no significant difference in the maximum phenylephrine dose according to COPD (p=0.438), asthma (p=0.263), or chronic lung disease (p=0.979). The effect sizes ($\eta 2<0.02$) were negligible or absent. The only factor with a few notable differences was nationality. Compared to Saudi patients, non-Saudi patients received, on average, lower doses of norepinephrine (p=0.021) and adrenaline (p=0.037). There were minimal effect sizes ($\eta 2<0.10$).

Based on analysis of this retrospective study sample, no other factors, including age, sex, BMI, or healthcare status, significantly influenced inotrope dosing patterns. More extensive prospective investigations are required to validate these null results. Among the respiratory conditions examined, chronic lung disease seemed to have the greatest effect on vasopressin and norepinephrine dosing patterns. Norepinephrine was also influenced by COPD. Effect sizes were generally greater in chronic lung disease. Disease status did not appear to affect the dosages of dobutamine or phenylephrine. Few correlations between demographic and clinical factors indicated that inotrope dosing in critically ill COVID-19 patients is primarily determined by clinical factors.

Analyzing the relationship between inotropic doses and demographic/clinical factors:

Additional analyses explored relationships between inotropic/vasopressor doses and demographic characteristics including age, sex, and BMI. One-way ANOVA tests found no significant differences in any drug doses based on age categories. This suggests age did not markedly influence inotrope dosing, though larger studies are needed(table 3). Similarly, independent samples t-tests revealed no significant dose differences between males and females for any drug. One-way ANOVAs also produced non-significant results according to BMI categories, indicating overall adiposity did not alter inotrope dosing.

Table. 3. Relationships between inotropic doses and demographic/clinical factors.

Factor	Drug	Results
Age	All drugs	No significant differences
Sex	All drugs	No significant differences
BMI	All drugs	No significant differences
Nationality	Epinephrine dose	Significantly lower in non-Saudis (p=0.037)
Norepinephrine dose		Mean dose: 1.39 vs 2.14 units
		Significantly lower in non-Saudis (p=0.021)
		Mean dose: 73.57 vs 101.37 units
Healthcare worker status	All drugs	No significant differences

Nationality was the only factor to show some impact, with maximum epinephrine and norepinephrine doses significantly lower in non-Saudis compared to Saudis. For epinephrine, non-Saudis received a mean dose of 1.39 units versus 2.14 units for Saudis. For norepinephrine, doses were 73.57 units for non-Saudis and 101.37 units for Saudis. While effect sizes were small, this hints genetic or cultural factors may subtly impact pharmacokinetics between populations. Healthcare worker status did not significantly influence any inotrope/vasopressor doses according to independent samples t-tests. Few consistent relationships emerged between characteristics and doses. More complex modeling accounting for genetic and biomarker factors in larger cohorts may help uncover subtler pharmacological determinants and residual variability not explained by clinical status alone.

Discussion:

This single-center retrospective study examined the relationship between respiratory conditions and inotropic agent doses in COVID-19 patients requiring admission to the intensive care unit and mechanical ventilation(Gnanenthiran et al. 2022; Gurin et al. 2021; Jain, Kashyap, and Singh 2021). Overall, the data indicate that, based on observed variations in administration patterns and moderate effect sizes, chronic lung disease may have the greatest impact on vasopressor and norepinephrine dosing requirements. COPD also showed a lesser extent of influence over norepinephrine dosage. We found important parallels between the conditions. As an illustration, chronic lung disease showed a substantial effect on norepinephrine and vasopressin dosage that was not observed in COPD or asthma(Gurin et al. 2021; Jain, Kashyap, and Singh 2021). This is consistent with the progressive character of chronic lung disease, which affects gas exchange and lung mechanics more than other conditions. Therefore, more severe hypoxemia and hemodynamic disturbances may explain the observed dosing modifications in patients with chronic lung disease(Jain, Kashyap, and Singh 2021; Jamali, Sinaei, and Razi 2023). Overall, the effect sizes were small. Despite statistically significant differences, respiratory status could clinically explain a maximum of 6-15% of the dosage variation. This suggests that other factors dominate initial drug optimization in critically ill COVID-19 cohorts and that the presence of the disease alone did not significantly alter inotrope management(Jamali, Sinaei, and Razi 2023). Additionally, the data imply that respiratory comorbidity profiles have little effect on some medications. There were no appreciable dose variations for phenylephrine, dopamine, or epinephrine depending on the presence of COPD, asthma, or other chronic lung diseases. Given the variable pharmacokinetic considerations among agents, this preliminary finding warrants further research.The small sample size and statistical power may have led to the lack of significant relationships with demographic influences(Jamali, Sinaei, and Razi 2023; Jordaan et al. 2021).

Nationality had the largest effect, with non-Saudis receiving much lower doses of norepinephrine and adrenaline than Saudis, albeit not significantly. This suggests that genetic profiling could potentially increase dosage in certain groups, but further research is necessary. Overall, research suggests that, in accordance with bedside

critical care practice guidelines, clinical disease variables largely determine the initial COVID-19 inotrope dosage(Jordaan et al. 2021; Kocayiğit et al. 2021). Sample limitations likely led to the missing of some dosing factors, such as biomarker correlations and pharmacogenomic signatures, which warrant further investigation—ideally through larger prospective studies(Tonge et al. 2023; Wong et al. 2021). This retrospective analysis's single-center design, which could introduce selection bias, and its inability to account for all confounding variables are its limitations. Because the documentation in electronic health records is based on accuracy, measurement error is possible(Kocayiğit et al. 2021).

Restrictions on sample size reduced statistical power to identify weaker signals or interactions between models. Furthermore, causality cannot be deduced. Larger cohorts would help future research because they would allow multivariate modeling to separate effects and take into account more variables at once(Jordaan et al. 2021; Kocayiğit et al. 2021; Koliastasis et al. 2022). These variables could be genetic profiles, medications being taken at the same time, organ function parameters, and measures of how bad the illness is(Park and Nho 2023; Pourdowlat et al. 2021; Ramcharan et al. 2020; Sarfaraz et al. 2022; Shehab and English 2023). Mechanistic in vitro or in vivo pharmacokinetic studies can support clinical results by connecting phenotypes to COVID-19 pathophysiology(Koliastasis et al. 2022; Konukoglu et al. 2022; Kunal et al. 2020).

Additional clinical value may come from longitudinal follow-up that links initial inotrope dosing patterns to longer-term outcomes(Labaste et al. 2024; Lee et al. 2022; Lu et al. 2020; McArdle et al. 2021). Do certain regimens, for example, affect mortality risk, extubation success rates, or the length of stay in the ICU or hospital? Initial dosage optimization based on previous response profiles has the potential to influence the course of care and customize early management(Souza et al. 2021; Tagliaferri et al. 2021; Tang et al. 2021; Tastemel Ozturk et al. 2024). Based on past administration patterns, the results indicated that chronic lung disease may slightly alter the dosage requirements for some vasopressors and inotropes. The sample size limitations led to the discovery of few relationships involving demographic characteristics. In this vulnerable patient population, individualized critical care pharmacotherapy could be advanced with further investigation, taking into account broader clinical, genetic, and outcome factors.

Conclusion:

The study provided initial understanding of the connections between inotropic dosage and respiratory disorders in COVID-19 patients on mechanical ventilation. Based on dose differences and effect sizes, chronic lung disease seemed to have the greatest impact on vasopressin and norepinephrine requirements. Additionally, COPD was shown to have an impact on norepinephrine dosage. Overall, though, effect sizes were rather modest. Does not appear to have an impact on phenylephrine, dopamine, or epinephrine dosages. A few reliable correlations between demographic characteristics and dosage were found, however nationality had a slight effect on norepinephrine and adrenaline levels.

These results imply that, in the ICU context, clinical disease variables are the main determinants of initial COVID-19 inotrope optimization. The retrospective single-center design, the inability to account for all confounding variables, and the relatively small sample sizes that limit the power to identify more subtle relationships, however, limit the conclusions. To validate results and advance precision inotropic therapeutic approaches for COVID-19, more carefully planned prospective studies with larger cohorts, biomarkers, outcomes, and pharmacogenetic profiling are required. Optimized initial dosing strategies based on previous response profiles may eventually help customize care and influence clinical trajectories in this high-risk population, provided further research is conducted.

DECLARATIONS

Funding: 'This work was supported by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia [Grant No. **KFU242858**]'

Conflict of interest: The authors have no conflict of interest to declare.

Ethical statement: Not applicable as this review involves already published studies and no ethical issue.

Acknowledgment: The authors acknowledge the Deanship of Scientific Research at King Faisal University for obtaining financial support for research, authorship, and the publication of research under Research proposal Number (**KFU242858**)

Author contributions: All authors substantially contributed to the study, including drafting the manuscript, conducting literature searches, analyzing data, critically reviewing the manuscript, and approving the final version for publication.

Data availability: The data that support the findings of this study are available on request

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