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Critical Rounds

MICRO LABS LIMITED

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Remdesivir Data from NIAID Trial

INTRODUCTION

Late Friday, peer-reviewed findings were released from one of remdesivir 's main studies, possibly the most effective antiviral agent for COVID-19, which verified and expanded the topline results announced a month ago in a press release. Hospitalized patients with COVID-19 who received remdesivir had a median recovery time of 11 days versus 15 days with placebo (recovery rate 1.32, 95 percent CI 1.12-1.55, P<0.001), John Beigel, MD of the National Institute of Allergy and Infectious Diseases (NIAID), and colleagues reported.

Mortality estimates for the remdesivir group were lower by 14 days compared with placebo, but non-significant (HR for death 0.70, 95 percent CI 0.47-1.04), the authors wrote in the New England Journal of Medicine. Ironically, as researchers looked at outcomes on an 8-point ordinal scale, they noticed patients with a baseline ordinal score of 5 had a recovery rate ratio of 1.47 (95 percent CI 1.17-1.84), while patients with a baseline score of 7 had a recovery rate ratio of 0.95 (95 percent CI 0.64-1.42).

Many of these data were published on April 29 by the NIAID, albeit without more information including trust levels of 95 per cent. On May 1, the FDA voted to provide for the therapeutic usage of remdesivir under an authorisation for emergency usage. However, physicians and other scholars have also been clamoring for a more detailed study to better inform their clinical practice. For example, concerns were posed as to how different subgroups benefitted more from the medication than others.

David Aronoff, MD, of Nashville's Vanderbilt University Medical Center, who was not interested in the study, indicated that the medication tended to be more successful when offered to people who were not as severely sick early in the process of illness. He added this wasn't unexpected provided the mechanism of action of remdesivir as an antiviral that works by blocking replication of the virus.

Aronoff said the medicine doesn't impact the host but just the virus. That tends to cause significant issues late in the process of the disease is the reactive reaction to the original harm done by the infection. Aronoff compared the virus to an arsonist starting fires, and antivirals like remdesivir when the police try to apprehend the arsonist until they start further fires and that it doesn't know if the arsonist is while the house is on fire.

For this cause, it might be important to pair a medication to address the viral response with a medication to address the host response to cure the virus. Aronoff noted the pending NIAID ACTT-2 study, which would investigate combined treatment of remdesivir and anti-inflammatory medication, baricitinib, vs. remdesivir alone.

Study Details

The Adaptive Covid-19 Clinical Trial (ACTT-1) consisted of 60 study locations, covering 45 locations in the United States, as well as sites in Europe and Asia. Participants infected with COVID-19 were assigned to either intravenous remdesivir or placebo for up to 10 days, with reports of lower respiratory activity. Primary outcome was time to recovery, meaning either hospitalization for infection control purposes only or discharge from the hospital.

An objective health and protection review board suggested unblinding the findings from 1,059 patients based on provisional evidence — 538 assigned to remdesivir and 521 assigned to placebo. On April 28, only 391 patients in the remdesivir group and 340 patients in the placebo group had finished the study (either survived or died) on day 29. Patients were 59 years and almost two-thirds were males, 53% were white, 23% were Hispanic or Latino and 21% were black. About 80 percent is registered at North American sites. Lots of patients reported two or more pre-existing illnesses, while lots reported asthma, 37% had obesity and 30% had diabetes mellitus.

Beigel and colleagues used 33-day Kaplan-Meier curves for recuperation within oxygen-categorized subgroups. For patients consuming oxygen but not at elevated flow or through non-invasive mechanical ventilation, the greater distinction between the remdesivir and placebo groups (i.e., the greatest medication benefit) was found. There was no improvement in recovery levels for remdesivir in high-flow oxygen patients or those on mechanical ventilation or extracorporeal oxidation of the membrane.

A tendency towards gain with remdesivir was apparent in patients not consuming oxygen, but it did not achieve statistical significance, possibly because more than 80 per cent of the placebo population benefited in this segment. There was no subgroup which clearly outperformed remdesivir by placebo. Some individuals (such as ethnic minorities) didn't have many patients to display major disparities. Notably, however, redesivir benefited patients with a symptom duration greater than 10 days just as much as those with shorter duration.

Serious adverse events occurred in 21 percent of remdesivir patients and 27 percent of placebo patients, and two in each group were judged to be related to the study drug. The most frequent adverse effect in the remdesivir population was anemia or reduced hemoglobin (7.9 per cent vs. 9.0 per cent in placebo community). In the remdesivir community too, pyrexia and hyperglycemia happened more regularly.

Aronoff said more would be understood after the study's final findings are announced in a few weeks ' time, although they are expected to validate the current research. When asking whether it would be acceptable to use this drug outside of a clinical trial environment, he acknowledged that there are reasons to pause, including the supply of remdesivir, the optimum treatment period, and that it can only be prescribed intravenously. Aronoff said whether you are at a care home or someone's place, it's hard to enforce anything very early. This is neither a panacea, nor a cure-all. It has several common impediments to its use. Gilead Sciences, maker of Remdesivir, performs two trials of its own for remdesivir, one of which includes placebo control. Results from that trial are expected soon.

Source: Beigel JH, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. N Engl J Med. May 22, 2020; doi: 10.1056/NEJMoa2007764

Role of acyl carnitines as biomarkers of mortality in out of hospital cardiac arrest patients

INTRODUCTION

Out-of-hospital cardiac attack (OHCA) is one of the leading causes of mortality of patients worldwide, with a heavy rate of neurological morbidity. For OHCA patients early risk stratification is critical and can affect professional decision-making. Various parameters for predicting mortality and neurological outcome after cardiopulmonary resuscitation have been studied for this purpose. For example, several clinical scores based on parameters gathered during cardiac arrest have been developed.

Furthermore, there is an increase in blood tests that may offer accurate details on the extent of the cardiac arrest injury suffered. Many research has explored inflammatory markers, heart markers, kidney markers and markers of brain injury in this context, among others.

In addition, there is an interest in novel metabolomics markers which can include additional knowledge about the distinct pathways involved in adverse outcome physiopathology after OHCA. A novel class of metabolomic markers analyzed in the sense of risk prediction are acyl carnitines (ACs), which are the esterified form of carnitine that mimic beta-oxidation, and function as an energy source. Carnitine is a quaternary compound of ammonium which is involved in fatty acid metabolism. After being transported through the mitochondria these serve as an essential source of energy. The clearing of short- and medium-chain ACs occurs in the renal system resulting in elevated rates of ACs in patients with renal insufficiency and pain. Previous work in sepsis patients shows that ACs are correlated with sepsis incidence and aetiology, and with sepsis-related mortality.

Additionally, there is increasing concern in ACs as important biomarkers in the field of cardiology. Among angina pectoris patients, levels of AC have been associated with an increased risk of cardiovascular death. In patients with heart failure who did not recover, and who had disease development, ACs were also decreased. Several pathophysiological mechanisms have been discussed, including an effect of ACs on the coagulation system, the metabolic system with increased insulin resistance, and hepatic encephalopathy. To the best of our knowledge, though, in the context of cardiac arrest, there is a lack of studies investigating the prognostic yield of ACs. The research aimed at exploring correlations of different ACs with result in patients with OHCA. Specifically, 39 different AC organisms were studied using a metabolomics technique, which varies in their fatty acid chain and saturation by the total amount of carbon atoms. Several ACs were hypothesized to have a predictive effect on negative health outcomes such as mortality or poor neurological performance.

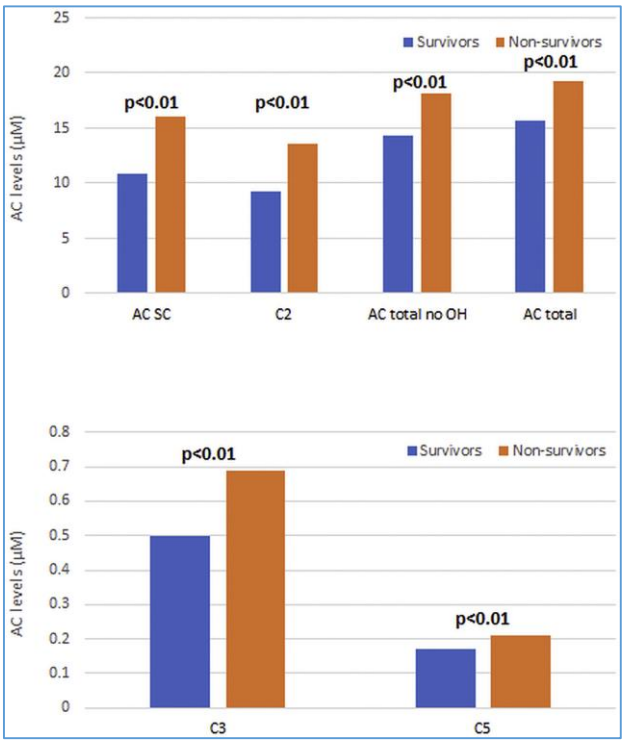
METHODS

We consecutively included OHCA patients in this prospective observational study upon admission to the intensive care unit. Westudied the association of thirty-nine different ACs measured at admission and 30-daymortality (primary endpoint), as well as neurological outcome at hospital

discharge (secondary endpoint) using the Cerebral Performance Category scale. Multivariate models were adjusted for age, gender, comorbidities and shock markers.

RESULTS

Of 281 included patients, 137 (48.8%) died within 30 days and of the 144 survivors (51.2%), 15 (10.4%) had poor neurological outcome.While several ACs were associated with mortality, AC C2 had the highest prognostic value for mortality [fully-adjusted odds ratio 4.85 (95%CI 1.8 to 13.06, p b .01), area under curve (AUC) 0.65] and neurological outcome (fully-adjusted odds ratio 3.96 (95%CI 1.47 to 10.66, p b .01), AUC 0.63).



Levels of different ACs stratified according to the primary endpoint.

CONCLUSIONS

The study findings show that higher serum levels of short-chain ACs such as C2, C3, and C5 as well as the number of all AC species was associated with higher 30-day mortality and lower neurological outcome for post-OHCA patients. ACs may also theoretically be used as prognostic indicators and may help to clarify the pathophysiology of the cardiovascular mechanisms underlying it.

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Relation between hospital occupancy, intensive care unit transfer delay and hospital mortality

INTRODUCTION

In the US, intensive care units (ICU) compensate for 13% of healthcare expenses, 4% of total health spending, and 1% of gross domestic product. Availability limitations generate inefficiencies in ICU patient flow with growing demand for urgent treatment, sometimes manifesting as referral delays to intensive treatment, or embarking in an unexpected ICU. Patients found eligible for discharge, but who stay in the ICU, by blocking entry to pending admissions add to capability pressure. 22–49 percent of ICU patients are estimated to experience delay in outward transfer from intensive care, primarily due to non-availability of general ward beds during periods of high hospital occupancy. Intensive care shortages contribute to a spike in ICU and hospital. Duration of treatment, including hospitalization expenses. From a glimpse perspective, it does not bring much benefit to the consumer and is called waste. The Australian Council on Health Care Standards considers ICU transfer delay to be a key performance indicator for acute hospital service delivery, and the United Kingdom Intensive Care National Audit and Research Center tracks it as a quality measure. Although the clinical and financial ramifications of prolonged ICU stay are evident, little is known regarding the patient-level effects. Considering the correlation with health satisfaction as a quality measure will support the case for or against ICU transition extension. Two prior studies from single-center, closed-model medical ICUs in the USA have shown contradictory results and their findings have not been replicated in other ICU types.

The objectives of this study were to:

1) Evaluate the mathematical relationship between hospital occupancy and extended ICU stay at a hospital; and

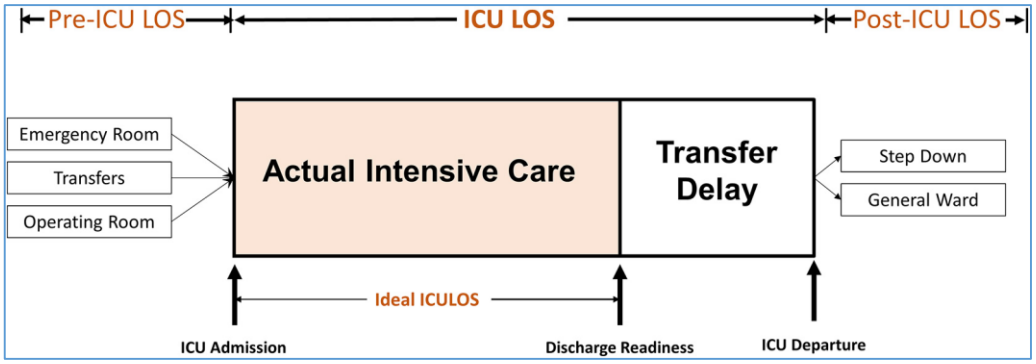
2) Determine whether ICU stay, in excess of what is deemed necessary, is associated with worse outcomes for critically-ill patients and whether this association, if present, varies by ICU specialty type.

The explanations for poor results of longer ICU stay when patients have completed medical procedures are more complex, as compared to patients whose entry into and eventual care in ICU are postponed. Hypothetically, patients undergoing external transition from ICU could be susceptible by providing lower acuity designations, lower nurse-to - patient ratios and therefore lower monitoring frequency; uncertainty in the established care of the patient between ICU and non-ICU physicians; and increased exposure to ICU stressors and complications like delirium, inadequate quality Sleep and MDR infections. Extended stay at ICU may also have an indirect impact on patient outcomes through other care processes. For starters, patients with delays in external transitions from intensive care might have been mistakenly released amid times of elevated ICU population, and sometimes wind up visiting the ICU after-hours and weekends — cycles of heightened risk for ICU patients. The hypothesis of this study was that higher hospital inpatient occupancy rates above a critical threshold, are associated with increasing transfer delays from intensive care and that intensive care patients with

longer transfer delays will have higher rates of in-hospital death and unplanned readmissions to the ICU, than patients with shorter transfer delays.

METHODS

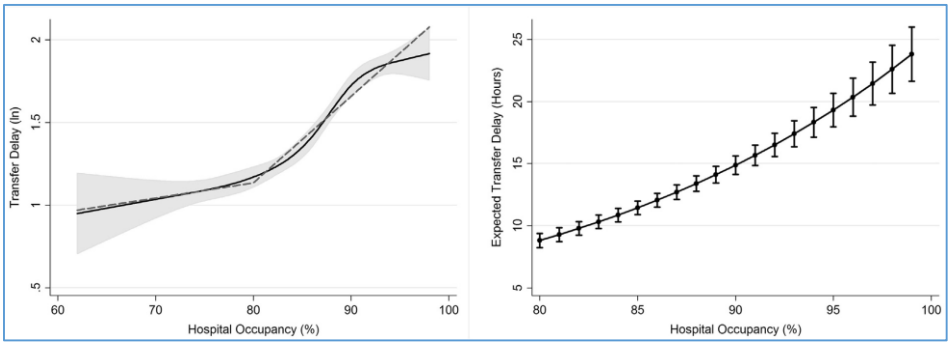
7-year retrospective cohort study of 8500 alive discharge encounters from4 adult ICUs of a tertiary hospital. We estimated associations between i) HospOcc and ICU transfer delay; and ii) ICU transfer delay and hospital mortality.



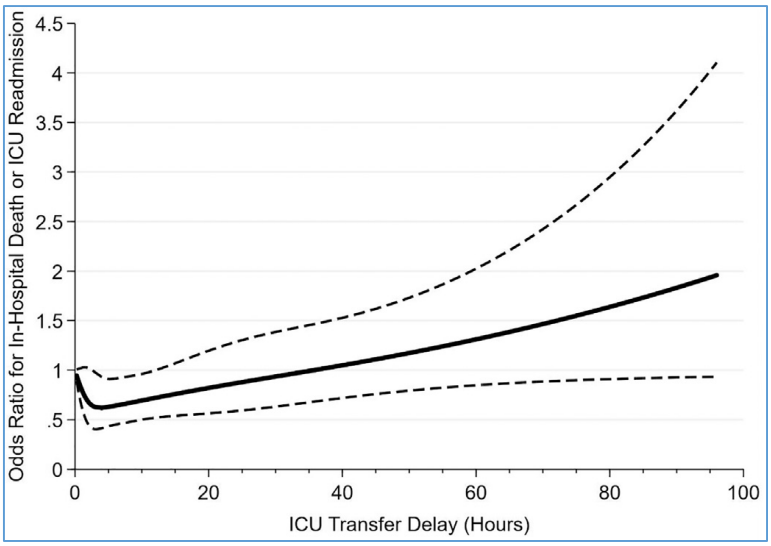
Intensive Care Patient Flow Schematic Illustrating Length of Stay and Transfer Delay.

RESULTS

Median (IQR) ICU transfer delaywas 4.8 h (1.6–11.7), 1.4% (119) suffered in-hospital death, and 4% (341) were readmitted. HospOcc was non-linearly related with ICU transfer delay, with a spline knot at 80% (mean transfer delay 8.8 h [95% CI: 8.24, 9.38]). Higher HospOcc level above 80% was associatedwith longer transfer delays, (mean increase 5.4% per % HospOcc increase; 95% CI, 4.7 to 6.1; P b .001). Longer ICU transfer delay was associated with increasing odds of in-hospital death or ICU readmission (odds ratio 1.01 per hour; 95% CI 1.00 to 1.01; P = .04) but not with ICU readmission alone (OR 1.01 per hour; 95% CI 1.00 to 1.01, P = .14).



Hospital Occupancy and Intensive Care Transfer Delay. Left Panel: Estimates are from a linear regression model using restricted cubic splines for the HospOcc variable. The linear regression fit on the natural log transformation of transfer delay with a restricted cubic spline for hospital occupancy (solid line) and the 95% confidence intervals (shaded grey band) are shown. The dashed line represents the piecewise linear fit with a knot for hospital occupancy at 80%. Right Panel: Graph line represents the expected mean ICU transfer delay and 95% confidence intervals for hospital occupancy levels 80% and greater.



Intensive Care Transfer Delay and Odds Ratio for In-hospital Death or ICU Readmission. Estimates are from a logistic regression model using a restricted cubic spline for the transfer delay variable. Odds ratios (solid line) and their 95% confidence intervals (dashed lines) were estimated and plotted for transfer delays ranging from 0.25 to 96 h.

CONCLUSIONS

Extended ICU stays can be correlated with decreased mortality following qualifying discharge. Identifying the vital occupation of hospitals at which ICU shift latency is substantially impacted will notify hospital operations and quality management measures to increase ICU capability burden. Such results would need to be repeated in different environments for ICU transfer delay to be considered a quality metric. Future work is required to clarify the mechanistic connections between delays in ICU transition and negative effects for patients with critical illnesses.

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