**Long-term acute care hospital outcomes of mechanically ventilated patients with COVID-19**

*(Electronic Supplementary Material)*

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**Methods**

*(Electronic Supplementary Material)*

**Study setting**

We conducted this double-center study at RML Specialty Hospital-Hinsdale (RMLSH-Hinsdale), a 115-bed free-standing LTACH, located in a Chicago suburb, and RML Specialty Hospital-Chicago (RMLSH-Chicago), a 69-bed free-standing LTACH located in Chicago. Two-thirds of beds in both institutions can be devoted to ventilator weaning.

During the COVID-19 pandemic, to increase the available intensive care unit (ICU) resources in the regional acute care hospitals, these LTACHs developed an organizational model similar to what was recently described by Grigonis et al (1). First, the two LTACHs, which have served the Chicago metropolitan area for more than 30 years, relied on the already well-established constructive and seamless working relationships with regional acute care hospitals. Second, the LTACHs maintain on-site High Acuity Units. If patients become unstable (e.g., hypotension requiring vasopressors, ventilator intolerance or agitation requiring intravenous sedation, acute gastrointestinal bleeding, septic shock) they are transferred into the High Acuity Units. Accordingly, these units help to minimize transfer to local acute care hospital ICUs. Patients in the High Acuity Units are directly attended by the LTACH critical care physicians. Thirdly, the two LTACHs accommodated as many mechanically ventilated patients with COVID-19 as possible via a series of organizational steps started in the early months of the pandemic. These steps included creation of separate COVID-19 isolation units with dedicated clinical staff, temporarily increasing patient-to-nurse ratio and patient-to-respiratory therapy ratio, contracting ancillary services from staffing agencies establishing a contractual agreement with the clinical laboratory of Loyola University Medical Center to provide SARS-CoV2 PCR testing with fast turnaround times – all of this while ensuring staff and patient safety by providing necessary personal protective equipment (PPE) and use/preservation protocols, ventilator viral filters, restriction of use of nebulized medication, installing whole-room high-efficiency particulate air (HEPA) filters or negative pressure devices, and suspending family visits. (As of June 1, 2021, the final date of follow up, no institutional outbreaks of COVID-19 have occurred at either LTACH facility). In addition, as soon as COVID-19 vaccines became available, the LTACHs organized an immunization campaign within the two hospitals. The result was operating the two LTACHs at virtually full capacity for most of the last 12 months while maintaining average census that far exceeded any prior periods. Every effort was made to retain and recruit bedside clinical staff during the COVID-19 surge. These were challenging efforts because of staff attrition for demand by local and regional institutions, and high temporary pay rates by “agency” staffing providers.

**Study approval**

The local Institutional Review Board approved the investigation as an observational study, with concurrent data collection for which the need of informed consent was waived (FXL 004).

**Study cohort**

Between April 1, 2020 and March 31, 2021, 215 consecutive patients were transferred to the two LTACHs from local acute care hospitals following admission for critical illness related to COVID-19. One hundred fifty-eight of them were transferred to be weaned from prolonged ventilation (≥4 days plus tracheostomy) following acute respiratory failure caused by SARS-CoV2 pneumonia (2, 3). The median number of ventilator days prior to transfer was 35 (IQR 27.0 – 46.0 d). Clinical outcomes were monitored until June 1, 2021, the final date of follow-up.

To explore the impact of COVID-19 on weaning outcome, we compared a subset of COVID-19 patients (n = 56) to consecutive non-COVID-19 patients with acute lung injury (n = 56) as the reason for intubation (acute lung injury being the presumed mechanism of respiratory failure in patients with COVID-19) **(e-Table 3)** (4). Patient in the non-COVID-19 group had been admitted to our two LTACHs in the 12 months preceding the pandemic (from February 27, 2019 to February 29, 2020). Patients were matched for age, gender, race group and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (5) on LTACH admission (6).

**Demographics and admission clinical data**

We prospectively reviewed medical records and laboratory results for all patients admitted to RML-Hinsdale and RML-Chicago with laboratory-confirmed COVID-19. In these patients we recorded data on demographics, race (7), chronic comorbidities, length of stay and duration of mechanical ventilation in the acute care hospital of origin, vital signs, laboratory values on LTACH admission, and results of SARS-CoV-2 nasopharyngeal swab testing while in the LTACHs. When the datapoints of interest were missing, the investigators contacted the primary team caring for the patient to obtain that information (8). In addition, we computed severity of disease (APACHE II) at LTACH admission and basic mobility and self-care functioning scores (Activity Measure for Post-Acute Care (AM-PAC) Inpatient Short Form) (9)at LTACH admission and at LTACH discharge. For patients who died during the admission, the assessment of basic mobility and self-care functioning closest to the day of death was used as the final follow-up assessment. (Of the total of 158 patients, 2 patients stilled cared for in the LTACHs on the final day of follow up, were not included in this aspect of the study.)

The inpatient AM-PAC Short Form for basic mobility and self-care functioning, also known as “6-Clicks”, include six activities each (9). Basic mobility includes activities such as turning over in bed, sitting down on- and standing up from a chair, walking in the hospital room, and climbing 3 to 5 steps (9). Self-care - also referred to as daily activity - includes items related to upper and lower body dressing, eating, toileting, grooming, and bathing (9). The patient’s level of assistance with a given activity is scored on a scale going from 1 indicating that the patient is unable to perform the activity (total assistance required) to 4 indicating that the patient is completely independent in performing the activity. Hence, the raw scores range from 6 to 24, with higher scores indicating less functional limitation. Using ad hoc conversion tables, the two raw scores are standardized to a *t-Scale* score (9). The *t-Scale* score for basic mobility ranges from 16.59 to 57.68 and that for self-care ranges from 17.07 to 57.54 (9). A *t-Scale* score of 36.97 for basic mobility and 37.26 for self-care functioning equate to approximately 50% disability in the two respective domains.

The AM-PAC is a valid instrument (10, 11) with high inter-rater reliability (10, 12), and high test–retest reliability (10, 11). In a study of more than eighty-thousand inpatients, Jette et al. (11) reported that the minimal detectable difference indicating a minimum change beyond measurement error in a *t-Scale* score was 4.72 for basic mobility and 5.49 for self-care functioning; whether these minimum change values are clinically meaningful remains to be determined.

Postal codes were used to determine whether patients lived in areas where the percentage of low-income residents exceeds the Illinois benchmark of 29.4%, as defined by the Uniform Data System Mapper (13).

**LTACH stay**

**Complications and procedures.** Information regarding complications including tracheal bleeding defined as bleeding requiring blood transfusion or otorhinolaryngology consultation, health care-associated infections including ventilator associated pneumonia (14), catheter-associated urinary tract infections (14), gastrointestinal bleeding requiring blood transfusion, shock, de novo hemodialysis and results of repeated SARS-CoV-2 nasopharyngeal swab testing were recorded.

**Weaning.** For infection control purposes and staff concerns about potential institutional outbreaks, COVID-19 patients were weaned by progressive decrease in pressure support ventilation. This consisted of up to 12 hours of pressure support during the day followed by assist-control, volume-control ventilation at nighttime (15, 16). When patients were able to tolerate pressure support of 6 cm H2O for 12 hours, they were disconnected from the ventilator and allowed to breathe spontaneously through the tracheostomy in a T-tube provided with an exhalation high-efficiency particulate air filter. The cohort of non-COVID-19 patients was weaned with pressure support (same as for COVID-19 patients) or a tracheostomy collar as previously described (16, 17).

**Physical and occupational therapy.** During LTACH stay, patients underwent physical and occupational therapy 4-5 times a week. Factors such as  tolerance of physical and occupational therapy sessions, patient's participation and motivation, and clinical stability determined the frequency and duration of interventions.

**SARS-CoV-2 nasopharyngeal testing**. The presence of SARS-CoV-2 RNA during LTACH stay was determined by target capture and transcription-mediated amplification (TMA) assay (Aptima SARS-CoV-2 assay, Hologic Inc., San Diego, CA) of nasopharyngeal swab specimens. The targets amplified by the assay are two conserved regions of the Open Reading Frame 1ab (ORF1ab) section of the viral genome (ORF1ab region 1 and ORF1ab region 2) (18). The ORF1ab encodes the *orf1abpolyproteins*that are cleaved into several nonstructural proteins (NSP1-NSP16) by viral proteinases (19). Some of these nonstructural proteins are involved with viral RNA synthesis (20, 21). The limit of detection of the assay is 500 genomic equivalents per milliliter and 62.5 viral copies per milliliter (18). Testing during LTACH stay was performed to assess potential infectivity towards hospital personnel, to be prepared for an eventual discharge home or eventual transfer to another health care facility (nursing home, inpatient rehabilitation).

**Outcome measures**

Clinical outcomes of interest included: (i) respiratory status (ventilator dependence, spontaneous breathing), (ii) functional status (AM-PAC basic mobility and self-care functioning scores), (iii) location after discharge (home, nursing-home, rehabilitation hospital, acute-care hospital), (iv) LTACH mortality and (v) need for home mechanical ventilation. Clinical outcomes were monitored until LTACH discharge or no later than June 1, 2021, the final date of follow up. Patients were considered weaning successes when they breathed without ventilator assistance for at least five consecutive days by day 45 of LTACH admission (16). All other patients were considered weaning failures.

**Statistics**

Categorical variables are reported as percentages and continuous variables as medians and interquartile ranges (IQRs). Chi-squared or Fisher exact test were used for categorical variables as appropriate. Comparison of continuous variables between 2 subgroups was performed using the Mann-Whitney U test. Statistical significance was assumed at 2-tailed p values of less than 0.05. Sample size and power calculations were not feasible owing to the lack of published data on LTACH outcomes for this new illness (22). Accordingly, sample size was equal to the number of COVID-19 patients transferred to the LTACHs during the study period (8, 23-25). All analyses were done using SPSS®23 (IBM SPSS, Armonk, NY). The analyses have not been adjusted for multiple comparisons (23, 26) and given the possibility of type I error, the findings should be interpreted as exploratory and descriptive (23).

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| **e-Table 1. Distribution of residence in low-income areas according to patients’ ethnicity**  |
| ***Ethnicity*** | **Residence in low income area**a |
| *Yes* | *No* |
| Hispanic  | 51 (68.9%) | 23 (31.1%) |
| Black  | 27 (75.0%) | 9 (25%) |
| White  | 14 (35.9%) | 25 (64.1%) |
| Other | 2 (22.2%) | 7 (77.8%) |
| Total | 94 (59.5%) | 64 (40.5%) |
| Data are n (%)a Areas where the percentage of low-income residents exceeds the Illinois benchmark of 29.4%, as defined by the Uniform Data System Mapper |

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| **e-Table 2. Published LTACH outcomes in non-COVID-19 patients** |
|  | Number study participants | Weaning success rate | LTACH Mortality |
| Scheinhorn et al 1997 (27) (USA) | 1,123 | 55.9% | 28.8% |
| Carson et al 1999 (28) (USA) | 133 | 38% | 50% |
| Vitacca et al 2001 (6) (Italy) | 52 | 73% to 77% | 7.6% to 11.5% |
| Schonhofer et al 2002 (29)  (Germany) | 403 | 68% | 24.3% |
| Pilcher et al 2005 (30) (UK) | 153 | 38% | 27% |
| Linton et al 2006 (31) (Israel) | 27 | 44.4% | 25.9% |
| Scheinhorn et al 2007 (32) (USA) | 1,419 | 54.1% | 25.0% |
| Polverino et al 2010 (33) (Italy) | 3,106 | 66% to 87% | 9-15% |
| Hannan et al 2013 (34) (Australia) | 78 | 78.2% | 10.2% |
| Jubran et al 2013 (16) (USA) | 316 | 44.7% to 53.1% | 10.0% to 14.5% |
| Sansone et al 2017 (35) (USA) | 437 | 73% | 36% |
| Kahn et al 2018 (36) (USA) | 9,447 | NR | 34.8% |
| Windisch et al 2020 (37) (Germany) | 11,424 | 64.3% | 14.5% |
| Jubran et al 2019 (17) (USA) | 315 | 53.7% | 16.5% |
| *Definition of abbreviations:* LTACH, long-term acute care hospital; NR, not reported |

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| **e-Table 3. Exploratory sub-group analysis of patients with and without COVID-19 and respiratory failure due to acute lung injury** |
| **Characteristics** | COVID-19 patients(N=56) | Non-COVID-19 patients (N=56) | *P* valuea |
| Age, years | 63.5 (55.0-73.8) | 62.5 (56.0-72.0) | 0.923 |
| Gender, F/M (%F) | 19/37 (33.9%) | 19/37 (33.9%) | 0.999 |
| BMI | 28.3 (25.9-32.3) | 26.4 (21.5-32.8) | 0.026 |
| **Race group** |  |  |  |
|  Hispanic and Black | 36 (64.3%) | 38 (67.9%) | 0.690 |
|  -Black  | 15 (26.8%) | 27 (48.2%) | 0.019 |
|  -Hispanic | 21 (37.5%) | 11 (19.6%) | 0.036 |
|  White Non-Hispanic | 18 (32.1%) | 18 (32.1%) | 0.999 |
|  Asian and other  | 2 (3.6%) | 0 (0%) | 0.153 |
| APACHE II | 13.0 (9.0-18.0) | 13.0 (9.0-19.0) | 0.771 |
| **Comorbidities** |
| Hypertension | 42 (75.0%) | 26 (46.4%) | 0.002 |
| Diabetes mellitus | 33 (58.9%) | 25 (44.6%) | 0.130 |
| Obesity (BMI ≥ 30) | 20 (35.7%) | 18 (32.1%) | 0.690 |
| Cardiac disease | 13 (23.2%) | 19 (33.9%) | 0.209 |
| Pulmonary disease | 8 (14.3%) | 21 (37.5%) | 0.005 |
| Malignancy | 5 (8.9%) | 8 (14.3%) | 0.376 |
| Hemodialysis | 4 (7.1%) | 5 (8.9%) | 0.999 |
| **Course in the acute care hospital of origin** |
| LOS, days | 40.0 (32.0-48.0) | 25.5 (20.0-33.8) | <0.0001 |
| Invasive MV, days | 34.5 (25.3-43.8) | 22.0 (15.0-30.5) | <0.0001 |
| Time to tracheostomy, days | 23.0 (18.0-27.0) | 14.0 (8.5-17.0) | <0.0001 |
| **Course in the LTACHs** |
| Weaning success, n (%) | 41 (73.2%) | 35 (62.5%) | 0.225 |
| Weaning duration(successes only) | 8.5 (4.0-18.3) | 7.0 (5.0-14.0) | 0.918 |
|  Mortality | 6 (10.7%) | 7 (12.5%) | 0.768 |
| *Definition of abbreviations:* F, female; M, male; BMI, body mass index; LOS, length of stay; MV, mechanical ventilation; LTACH, long-term acute care hospital a Mann-Whitney U was used for continuous variables, and *Χ2* or Fischer exact test was used for categorical variables |

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| **e-Table 4. Published mechanical ventilation outcomes and mortality in acute ICU COVID-19 patients and current study** |
|  | Number of patients on mechanical ventilation | Duration of follow up | Weaning success rate | Duration of MV in survivors (days) | Mortality† |
| King et al. (38) (USA) | 164 | Right-censored 8.19.2020 | NR | 14.6 (± 12 SD)  | 42.7% |
| Botta et al. (39) (Netherlands) | 553 | Hospital day 28 | 48% | 16·5(IQR 10·5–26·5) | 35% |
| Yang et al. (8) (China) | 37 | Hospital day 28 | 11% | NR | 81% |
| Zangrillo et al. (40) (Italy) | 73 | Hospital day 19(IQR 15.0-27.0) | 31.5% | NR | 23.3% |
| Cummings et al. (24) (USA) | 203 | Right-censored 4.28.2020(at least 28 days) | 26% | 27.0(IQR 15.0-32.0) | 41% |
| Auld et al. (41) (USA) | 165 | Right-censored5.7.2020 | 56.7% | NR | 33.9% |
| Ferrando et al. (42) (Spain) | 742 | Hospital day 28 | 57.8% | 14.0(IQR 7.0-24.0) | 32% |
| Doidge et al. (43) (UK) | 7,912 | Right-censored10.1.2020 (at least 60 days) | NR | 18.5 ±9.1 (SD) | 44.5%\* |
| Camporota et al. (44) (UK) | 213 | ICU day 30 | NR | 15(95% CI 13.5-16.5) | 34.2% |
| Baedorf Kassis et al. (45)  (USA) | 40 | Until in-hospital death, tracheostomy placement, or extubation and hospital discharge  | 65% | 14.5(IQR 9.5–19.0) | 32.5% |
| Bain et al. (46)  (USA) | 27 | 60 days post-admission  | NR | 13.5(IQR 8.0 -18.0) | 44% |
| Gamberini et al. (47) (Italy) | 391 | 28 days post- intubation | 53.2% | 14.0(IQR 9.0–19.0) | 36% |
| Current LTACH study  (USA) | 158  | Right-censoredJune 1, 2021 (at least 45 days) | 70.9%  | 51.5 (IQR 39.3-66.8) | 9.6% |
| *Definition of abbreviations:* MV, mechanical ventilation; SD, standard deviation; IQR, interquartile range; NR, not reported; CI, confidence interval; LTACH, long-term acute care hospital† ICU mortality unless specified otherwise \* In-hospital mortality |