A Narrative Account of Nottingham University Hospitals NHS Trust Critical Care Response to the COVID-19 Pandemic, and Analysis of Outcomes

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A narrative account of Nottingham University Hospitals NHS Trust critical care response to the COVID-19 pandemic, and analysis of outcomes

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Abstract

Background

The novel coronavirus SARS-CoV-2 and associated multisystem disease COVID-19 originated in Wuhan, China in December 2019. The resultant pandemic has resulted in an unprecedented strain on healthcare services around the world, including the greatest challenge seen by critical care medicine in modern times. This narrative illustrates the response of Nottingham University Hospitals NHS Trust critical care department to the crisis, including resource allocation and clinical management strategies and illustrates patient outcome for those admitted to critical care during the first pandemic wave.

Methods

Patients admitted to critical care whom tested positive for SARS-CoV-2 between March-May 2020 were identified for retrospective case review as part of service evaluation. Clinical, laboratory and radiological data was collected. This included patient level data on ventilation and fluid balance.

Results

During the three period March-May 2020, retrospective case review showed 109 patients admitted to critical care with COVID-19. 88 (80.7%) of the 109 patients received mechanical ventilation, 21 (19.3%) patients received renal replacement therapy. Critical care mortality was 26 (23.9%) patients and hospital mortality was 27 (24.8%) of the 109 patients.

Conclusion

This mortality rate was an unexpected finding based on early literature and help to provide a baseline for comparison hereafter. Commentary is provided for several aspects of care that may account for the low mortality rate and warrant further investigation in the future.

Keywords

COVID-19, SARS-CoV-2, ventilation, renal replacement therapy, thrombosis, mortality

Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from Wuhan, China in December 2019,(1) with its progression to the coronavirus disease 2019 (COVID-19)(2) global pandemic has presented the greatest worldwide challenge to critical care medicine since the origin of the speciality during the 20th century polio epidemic.

With over 36 million cases and 1 million deaths globally,(3) the logistical obstacles and influx of patients, alongside a rapidly evolving understanding of a novel disease, have triggered the largest

concerted effort by healthcare systems across the globe on a scale unwitnessed by most practising clinicians. Given the paucity of published research to inform clinical decision making early on in the pandemic, it is unsurprising to see mortality rates, for those ventilated in critical care, over 50%,(4-7) and in some instances approaching 90%.(8, 9)

To date, minimal outcome data from individual UK intensive care units is available. More recent data suggest mortality rates are improving,(10-12) as patient numbers decline coupled with better understanding how to treat those critically ill with COVID-19.

Given the wide variation in COVID-19 ICU mortality,(13) the authors describe the approach of their critical care department to this crisis; including logistics, resource allocation, and clinical management strategies; and finish with an analysis of our outcomes, with the aim to disseminate our findings and add to the stock knowledge of the subject in anticipation of further surge in COVID-19 incidence.

Methods

The proposed method of retrospective observational analysis of routinely collected anonymous data was registered as a service evaluation with the NUH clinical effectiveness department (reference 20-314C).

All patients admitted to Nottingham University Hospitals critical care (NUHCC) department between 10th March 2020 and 31st May 2020 who tested positive for SARS-CoV-2 were identified. Medical records of these patients were retrospectively reviewed. The demographic and clinical data required for submission to the Intensive Care National Audit and Research Centre (ICNARC) was combined with observation recordings, laboratory results and radiology reports.

Ventilation data was obtained from manual search of the 0800 and 2000 time points for the first 7 days of mechanical ventilation, and fluid balance reviewed from admission to the earliest occurrence of renal replacement therapy, discharge (including death) from critical care, or day 10 of critical care treatment. Data collection was carried out by the authors working on critical care during the COVID-19 pandemic.

Critical Care at Nottingham University Hospitals NHS Trust

Nottingham University Hospitals (NUH) NHS Trust is a large tertiary hospital in the United Kingdom, with around 1700 acute care beds across two sites – The Queen’s Medical Centre (QMC) and The Nottingham City Hospital (NCH). The emergency department receives over 180 000 attendances per year. NUH serves as the regional major trauma and neurosciences centre, providing acute and elective services to the 2.5 million residents of Nottinghamshire, and tertiary services to 3-4 million residents within the East Midlands.

Prior to the emergence of COVID-19, critical care at NUH was commissioned for 21 level 3 and 20 level 2 beds at QMC, and 17 level 2/3 beds at NCH and an additional cardiac critical care unit with capacity for 16 level 2/3 beds with around 4500 total admissions to critical care per annum.

Planning

Contingency planning, including segregation of current facilities into COVID-19 and non-COVID-19 areas with identification of potential locations for continued surge conditions, was underway in late February. The release of an email communication via the European Society of Intensive Care Medicine (ESICM) from Northern Italy,(14) served as a catalyst to accelerate preparations.

Reaching near capacity in an existing critical care area would trigger admission to sequential pre-identified isolated areas including operating theatre pod complexes. Surge plans were constantly reviewed and amended to adapt to the evolving situation. To minimise the number of geographically discrete critical care areas within the hospital, additional physical partitioning walls and gowning lobbies were rapidly constructed to provide cohort areas within existing open floorplan areas. This was in part made possible given the marked early reduction and subsequent cessation of elective surgical work, and transient fall in non-COVID-19 critical care admissions.

Reduction in elective work followed by its cessation on 12th March, as the first isolated COVID-19 cohort area was utilised, provided an opportunity of around two weeks prior to high frequency surge of COVID-19 admissions. This allowed for iterative development of local protocols, practical guides and checklists for donning and doffing personal protective equipment (PPE), conduct of rapid sequence induction (RSI) and intubation for respiratory failure, emergency assessment, retrieval and transfer of patients to critical care, and prone positioning. Critical care staff were targeted for FFP3 mask fit testing with drop in 'PPE clinics' for staff to familiarise themselves with donning and doffing procedures. Simulation training took place for all those involved in intubation, transfer and prone positioning of patients with suspected COVID-19 whilst wearing PPE appropriate for aerosol generating procedures (AGP).

Staffing

Critical care consultants

By mid-March a shadow rota for non-resident on-call consultants to be available day and night to provide additional cover as required was in place. On 30th March the shadow rota was combined with the general critical care rota to provide round the clock consultant cover. With 33 critical care consultants, there was the ability to allocate at least one to each of the critical care areas until 8pm, even at maximum surge capacity. In addition, there was an allocated lead consultant to co-ordinate referrals, transfers and beds. At each hospital site, overnight cover consisted of two consultants, one resident and one non-resident after 0200. The expanded rota allowed maintenance of our usual level of consultant involvement in daily clinical decision making and bed management on a day-to-day basis. All programmed activities (PAs) in alternate specialties for dual trained intensivists were utilised for direct clinical care (DCC) in critical care.

Anaesthetic department support

A full complement of emergency care, including adult and paediatric emergencies, trauma and obstetric lists was preserved throughout. All emergency and on-call tiers were covered with normal levels of staffing.

Early reduction in elective surgical workload meant there was sufficient liberation of anaesthetic trainees to support rotas in critical care. Consultant anaesthetists backfilled anaesthetic trainee on-call commitments 24-hours a day, with enhanced levels of on-call out of hours, both resident and non-resident. Anaesthetic teams were responsible for the rescue and transfer of emergency admissions from the emergency department to critical care, including inter-hospital transfer between the two hospitals within the trust.

Junior medical staff

Pooling of trainees from anaesthetics, medicine and academic training programmes allowed the number of whole time equivalent (WTE) trainees and fellows to be increased from 40 to 98 at peak capacity. Out of hours cover for each critical care area, including surge areas, comprised a minimum of two trainees at all times, at least one of whom with competence in advanced airway management and procedural skills appropriate to critical care.

Nursing staff

Around 350 registered critical care nurses work at NUH. They worked flexibly between sites and areas with increased oversight from the senior nursing team. With the support of theatre nurses and operating department practitioners (ODPs) they were able to provide one to one, nurse to patient, ratios. At maximum surge there was a minimum of one registered critical care nurse to two patients (supported by non-ICU nurses and ODPs).

Clinical

Guidance

Groups of senior nurses and consultants were established to agree and write clinical guidelines to allow critical care to be delivered by non-critical care staff in the event of a sustained surge. Version control was important given the rapid evolution of clinical knowledge, evidence base and subsequent changes in guidance. As a consultant body it was accepted that recommendations put forward by each group were reviewed for omissions and errors rather than a wholesale change in content, this was vital to ensure rapidity of dissemination and implementation. All guidance was reviewed by the critical care governance lead.

Ventilation

Initial ventilation guidance was formulated without any first-hand experience of managing COVID-19. It was focussed around the principles of managing acute respiratory distress syndrome (ARDS) and viral pneumonitis; with lung protective ventilation comprising a low tidal volume and high positive end expiratory pressure (PEEP),(15) paralysis,(16) and prone positioning for refractory hypoxia,(17) this was disseminated by 31st March.

Local experience of COVID-19 was not typical of the disease described in early literature,(4, 8, 18, 19) prompting the need for rapid evolution of the guidance with a significantly different approach by 9th April. This had features in common with recommendations from Guy's and St Thomas'.(20) The updated guidance suggested a starting PEEP of 0.1 cmH₂O.kg⁻¹, used a low PEEP-FiO₂ ladder, lung protective tidal volume and permissive hypercapnia to a pH of 7.15. SpO₂ target was 88-92%, and we strictly adhered to targeting SpO₂ rather than PaO₂. A summary of the ventilation strategy can be found in Appendix I.

Prone position ventilation was observed to markedly improve oxygenation and this was subsequently encouraged as an early intervention rather than rescue intervention for hypoxaemia. Dedicated prone positioning teams were used to facilitate this.

Initial national guidance advised the use of dry ventilation circuits with a heat and moisture exchange filter (HME) at the patient end.(21) Difficulties were encountered with saturation of the HME filter and with mucous plugging. By 11th April, practice was changed to allow consultant consideration of the use of warmed and humidified (water bath) breathing circuits after an initial time period with HME where risks of COVID-19 transmission was thought to be outweighed by the risk of adverse events from impaired HME filter performance.

NUH was asked to expand ventilator bed capacity to 186, the latest surge plan had accounted for 167 ventilated beds. At peak surge we had 57 simultaneous confirmed COVID-19 patients within critical care.

In addition to around 60 existing critical care ventilators, coincidental prior acquisition of replacement ventilators meant there were a further 50 available critical care ventilators to supply surge locations. The challenge of training staff on new ventilators and anaesthetic machines was undertaken on an accelerated timetable with the use of bespoke quick reference guides and face-to-

face sessions. The existing and new ventilators were cohorted at QMC and NCH respectively and this helped to minimise the population of staff requiring training on both machines. Expanded ventilator capacity meant that almost all patients with COVID-19 were ventilated with dedicated critical care ventilators.

Oxygen supplies were physically checked for each critical care area including surge area, and usage was monitored daily.

Tracheostomy

In anticipation of a large cohort of ventilator dependent patients with COVID-19, plans were drawn up to increase capacity for tracheostomy insertion. UK and international guidance,(22) suggested that delegation of tracheostomy insertion to the surgical teams seemed a prudent use of resources and may be preferable given concerns regarding infection control and aerosol generation during percutaneous tracheostomy.(23)

Given the local experience of over 200 percutaneous tracheostomy insertions per year within NUH critical care, decision for mode of tracheostomy insertion remained at the discretion of the critical care consultant. Updated procedural guidance was circulated suggesting that the routine modified percutaneous Ciaglia technique(24) was continued but altered to minimise aerosol generation by pausing ventilation during bronchoscopy and tracheal dilation and clamping of the breathing circuit prior to disconnection.

Fluid management and renal replacement therapy

Initially, a restrictive fluid approach was recommended, aiming for even to slightly negative daily fluid balance based on current practice.(15, 25) This was to be achieved using diuretics and renal replacement therapy (RRT) if required. As the ventilation guideline was changed, so our approach to fluid management was liberalised, aiming for euvolaemia, avoiding the use of diuretics and preserving RRT for the usual indications of acute kidney injury.

RRT during the COVID-19 surge was in keeping with routine local practice - continuous veno-venous haemo(dia)filtration (CVVH(DF)). In anticipation of high demand and in order to preserve filter and circuit consumables several non-routine recommendations were made – routine left internal jugular central line insertion, preserving the right internal jugular for wide bore dual-lumen RRT cannulae. A higher proportion of pre-dilution (70%) was preferred. The effluent rate prescribed was maintained at 35ml.kg⁻¹.hour, but as the consumables supply chain was stretched a dose of 25ml.kg⁻¹.hour was preferred. Low molecular weight heparin (LMWH) remained the first line anticoagulant of choice (Appendix II). NCH has the water supply, staffing and equipment to deliver intermittent haemodialysis, this became a valuable resource as the pandemic stretched the supply chain of CVVH consumables.

Pharmacological thromboprophylaxis

Early observation showed COVID-19 patients with frequency of thrombotic complications exceeding those anticipated in normal practice. Fastidious weight-based augmentation of thromboprophylaxis preceded collaboration with haematology (9th April) and subsequent Factor-Xa guided higher doses thromboprophylaxis for COVID-19 patients in critical care on 30th April (Appendix III). Therapeutic anticoagulation was reserved for those with either demonstrated or high suspicion of thromboses where clinical instability precluded cross sectional contrast imaging.

Rationalisation of medication

Pharmacy support was increased to provide seven-day cover for the duration of the pandemic surge. Use of routine agents was dictated by national and local availability and procurement. Propofol was

spared for critical care by encouraging the use of volatile anaesthesia intraoperatively. The local sterile production unit provided support by supplying batches of ready to use infusions such as noradrenaline and insulin. Where compatibility data existed, drugs were drawn into the same syringe to conserve consumables and infusion devices, such as combined morphine and midazolam. As soon as practicable, intravenous sedation was changed to enteral sedation to further liberate infusion devices.

Rehabilitation

Each surviving patient with COVID-19 was discharged to what became a bespoke dedicated rehabilitation unit. There was input from the respiratory and rehabilitation team, with specialist physiotherapy, speech therapy, occupational therapy, psychology and weekly input from critical care until ready for discharge home.

Research

NUH recruited patients to the REMAP-CAP,(26) RECOVERY,(27) ISARIC,(28) and GenOMICC(29) studies, three of which were already open. No patient received experimental treatment outside a clinical trial.

Ethical principles

Visiting was restricted in line with national guidance.(30) Daily routine structured telephone updates were provided to families. End of life discussions were led by consultants in person where possible. Small numbers of next of kin were allowed pre-arranged visits to patients under 18 years of age, and as part of end of life care, provided they themselves were not required to isolate.

A sub-group of consultants produced guidance considering the ethics of distributive justice,(31) faced with the real possibility of demand outstripping available resource. On the whole, normal criteria for critical care referral, assessment and admission were maintained, broadly consistent with NICE guidance.(32) There were no occurrences where critical care was denied on the basis of capacity. Local resource availability facilitated inter-hospital transfers within the critical care network to alleviate some pressure on local ICUs.

Results

During the time period between 10th March and 31st May 2020, there was in excess of 33 000 attendances to acute admission wards and the emergency department, including over 4000 patients with suspected COVID-19. There were 1250 patients with confirmed COVID-19.

In total 109 patients were admitted to critical care with positive real-time reverse transcriptase–polymerase chain reaction (rRT-PCR) SARS-CoV-2 infection from respiratory tract samples. This included 3 patients transferred in from network critical care units. Date of censoring for follow-up was 5th June.

Baseline demographics and indicators of acute severity are shown in comparison with national data from ICNARC in Table 1.

A total of 84 (77.1%) patients had at least one underlying medical comorbidity. The most common comorbidities were hypertension (50 patients, 45.9%), obesity ([Body mass index (BMI) >30] 47 patients, 43.1%), diabetes mellitus (32 patients, 29.4%), hyperlipidaemia (21 patients, 19.3%) and asthma (17 patients, 15.6%). A median of 3 (IQR, 3-4) organ systems were supported. Median and mean APACHE II score was 15.

Initial laboratory investigations are presented in Table 2. Leukocyte count at admission of greater than $11.0 \times 10^9.L^{-1}$ was present in 31 (28.4%) patients. Lymphocyte count of less than $1.0 \times 10^9.L^{-1}$ was present in 68 (62.4%) patients. Elevated CRP was present in all 109 (100%) patients. Peak CRP during ICU stay was a median of 333 mg/L (IQR, 215-385). Peak ICU D-Dimer value was 2000 $\mu g.L^{-1}$ (IQR, 1072-5327). A lactate greater than 1.6 mmol.L⁻¹ was present in 36 (33.0%) patients on admission.

Thrombotic complications were diagnosed in 15 (13.8%) patients. The majority of these were pulmonary emboli, in 9 (60%) of the 15 patients. Large vessel venous thrombosis was seen in 3 (20%) patients and evidence of thrombotic stroke in 5 (33.3%) patients. Both pulmonary embolism and thrombotic stroke was demonstrated in 2 of 15 patients (Figure 1).

Ventilation

88 of the 109 critical care COVID-19 admissions received invasive mechanical ventilation. Outcome data was present for 79 patients, the paper based 24-hour charts were available for 55 patients. In total 2 (2.27%) patients were transferred for extracorporeal membrane oxygenation (ECMO).

Median duration of ventilation for survivors was 19 days (IQR, 9-27), and 10 days (IQR, 5.8-12.8) for non-survivors (Table 3). Summary of the first seven days data for ventilation (Table 4) shows a reduction in PEEP, mean airway and peak pressure after the change in ventilation strategy. The median tidal volumes overall were 7.1mL.Kg⁻¹(IQR, 6.2-8.3), median driving pressure was 14cmH₂O (IQR, 11-16). 22 (40%) of 55 patients were ventilated in the prone position, and 36 (65%) patients received an infusion of non-depolarising muscle relaxant during the first seven days of ventilation.

Tracheostomy

41 (47%) of the 88 invasively ventilated patients received a tracheostomy. 32 (78%) were inserted percutaneously with the remainder surgical. Excluding the 2 patients who received ECMO, these were inserted between days 8 and 31 (median 14 days, mean 15 days). There were no tracheostomy associated deaths.

Fluid balance and renal support

The proportion of patients requiring RRT for acute kidney injury (AKI) varied throughout the pandemic surge. In the first three weeks of admissions, 11 (32%) of 34 patients received RRT for AKI compared with 10 (15%) of 68 patients admitted in subsequent weeks. The seven-day median daily fluid balance for patients admitted to ICU with COVID-19 in the first three weeks was 138ml positive (IQR, -310 to 802) compared to 620ml positive (IQR, -44 to 1235) for patients admitted in subsequent weeks.

Outcomes

Critical care outcome data were available for 100 of 109 patients; cohort flow can be seen in Figure 2. Critical care mortality was 26 (23.9%) patients, critical care discharge was 74 (67.9%) patients, with 9 (8.3%) patients remaining in critical care. Of those 74 patients discharged from critical care, 68 (91.9%) patients have been discharged from hospital, 5 (6.8%) patients remained in hospital and 1 (1.4%) further patient died. Overall hospital mortality stood at 27 of the 109 patients (24.8%).

The median critical care stay for survivors was 13 days (IQR, 7-27) and for those who died was 8 days (IQR, 4-11). For survivors, the median hospital length of stay was 24 days (IQR, 15-36) compared to 11 days (IQR, 7-18) for those who died.

When considering those receiving invasive mechanical ventilation, outcome data was available for 79 of the 88 mechanically ventilated patients, 22 (27.8%) patients died in critical care and 57 (72.2%) patients were discharged from critical care. Hospital outcomes for 74 patients demonstrated no further deaths, 22 (29.7%) patients; and 52 (70.3%) patients had been discharged. The median duration of mechanical ventilation for survivors was 19 days (IQR, 9-27) compared to 10 days (IQR, 5.8-12.8) for those who died.

Outcomes by admission variables

Outcome by patient characteristics can be seen in Table 5. Mortality was higher in those above 60 years of age, with the highest mortality (43.5%) seen in the 60-69 year-old age group. The mortality rate in male and female patients with COVID-19 was 26.6% and 25% respectively. The difference observed was not as marked as in the national data (43.7% vs 36.5%).

The lowest mortality (20%) was seen in those of Asian ethnicity, followed by Caucasian (26.5%) and Black (30%). The highest mortality was in those of mixed ethnicity (50%) and those categorised as Other (50%) although numbers in these groups were small (2 and 4 patients respectively).

Considering patient BMI demonstrated those with a BMI of less than 25 kg.m⁻² had the highest mortality in our cohort at 37.9%. Lowest mortality (18.2%) was seen in those with a BMI between 30-40 kg.m⁻².

Figure 3 shows the number of COVID-19 admissions, APACHE II score, cumulative number of patients in critical care and mortality by week of admission. Mortality was higher for those admitted in the first 5 weeks (30-50%) compared to those admitted in the latter 7 weeks (0-9%). An increase in mortality for the latter weeks is to be expected as 9 patients remain in critical care. The distribution of those developing thrombotic complications shows 13 (86.7%) patients were admitted in the first 6 weeks of the period reviewed and 2 (13.3%) patients in the latter 6 weeks (Figure 1).

Discussion

Justification

Observed critical care mortality rate of this cohort was 23.9%, overall hospital survival was 75.2%. The observed mortality within this cohort appears to be lower than that previously published,(4-9) and is more in keeping with recent data published from ICNARC. This pessimism was based on a flood of information from various news and social media sources outside the normal channels for clinical information. The intention of this evaluation of experience and knowledge gained during the pandemic surge was to identify plausible factors that may explain the variation in outcome data and facilitate discussion to improve overall care to COVID-19 patients.

Interpretation

Early reduction and then relocation of elective surgical workload to alternative providers allowed invaluable time to prepare COVID-19 surge areas and perhaps more importantly allow for development of systematic and comprehensive training in procedures in AGP PPE including intubation, transfer, and prone positioning. Bespoke guidance was developed in house preceding national publication by some weeks.(33)

The highest number of simultaneously ventilated patients with COVID-19 was 57, this was well below the maximum planned surge capacity of 167, thus NUH critical care was not overwhelmed with patients suffering from COVID-19. Staff ratios always ensured one to one care, at peak occupancy there was one registered critical care nurse for two patients supported by additional non-critical care staff. Consolidation of trainee rotas provided trainees with requisite skills to be deployed into every surge area. Critical care consultant presence was maintained at all times, including out of

hours and every critical care patient was reviewed at least twice per calendar day by a critical care consultant.

Availability of critical care ventilators, surge capacity bed areas and staffing ratios mitigated the acuity of the resource strain and allowed for the delivery of critical care without the stress of nearing capacity and triaged admission policy.

An apparent reduction in critical care mortality, RRT and thromboses rate was observed following week six of the pandemic (Figure 1 and Figure 3). This was associated with changes in guidance for ventilation, RRT and thromboses, but may also reflect increased experience and familiarity with COVID-19.

Summary description of the ventilation parameters show similar median and mean averages for all parameters suggesting a paucity of outlier values. Tidal volume, driving pressure and peak pressure were always within ranges associated with survival benefit in ARDS.(34) Reduction of PEEP and subsequently mean airway, driving and peak pressure may have had a sparing effect on right ventricular function and global cardiac output.(35)

There was a marked reduction in the RRT rates as the pandemic progressed and coincided with an observed change in approach to fluid balance. Other plausible reasons may include preserved cardiac output with lower mean airway pressure, reduced use of RRT in pursuit of negative daily fluid balance and reduced intrarenal thrombus burden.

Decreased observed frequency of thromboses also occurred at around 6 weeks coinciding with an augmented thromboprophylaxis strategy, amended ventilation and RRT guidance.

Limitations

In-depth statistical analysis is not appropriate given the small cohort size and the heterogeneous nature of the patients and there are potentially many confounding factors that could influence mortality. However, when compared to published datasets patient numbers are comparable if not favourable.(4, 5, 7, 11, 12, 36)

Apparent improvement in mortality during the course of the pandemic surge may have occurred with increased exposure and familiarity in dealing with COVID-19 rather than as a result of evolution of clinical guidance.

Detailed ventilation data was missing in around one third of the patients due to delays in archiving paper-based notes or use of case notes by other teams.

Respiratory data collection was limited to seven days at two data points per day this was felt to be a good representation of the previous 12 hours of ventilation strategy and clinical condition.

Extrapolation

Submission of data to ICNARC has been essential for surveillance of critical care outcome data for the last 25 years, however collection of data on unit dependency, capacity, surge capacity and staffing levels could help to determine the interhospital variation in outcome and indeed seek to address inequalities between distribution of patients amongst hospitals in the same critical care network.

Collection and analysis of this patient cohort has provided the opportunity to establish baseline compliance with specifically produced guidance for the treatment of patients with COVID-19.

Mortality appeared to improve during the latter half of the pandemic surge, this may reflect a number of rapid adaptations to clinical guidance alongside increased clinical experience, whilst maintaining the staffing capacity and resources to deliver high quality care.

Conclusion

As the first COVID-19 pandemic surge subsides in the UK the authors share experiences and learning points which were associated with a high survival rate. Focus on a whole system approach to management of patients with COVID-19 has established baseline data and identified several facets of care that warrant extended investigation in the future.

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Declarations

Ethics approval and consent to participate

The proposed method of retrospective observational analysis of routinely collected anonymous data was registered as a service evaluation with the NUH clinical effectiveness department (reference 20-314C).

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available due to the information governance conditions of the institution further analysis is likely to be included in future research. Data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contribution

All authors collected, collated, analysed and interpreted the data. All authors wrote, read and approved the final manuscript.

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Author's interests

All four authors are Consultants in Critical Care Medicine at Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom and worked during the COVID-19 pandemic surge and were involved in the development of several of the guideline topics.

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Table 1. Baseline demographics and indicators of acute severity in patients admitted to Nottingham University Hospitals NHS Trust (NUH) critical care with confirmed coronavirus disease 2019 (COVID-19) with comparison to national data obtained from the Intensive Care National Audit and Research Centre (ICNARC). NUHCC - Nottingham University Hospitals Critical Care, SD - Standard Deviation, IQR - Inter-Quartile Range, APACHE II - Acute Physiology And Chronic Health Evaluation II, PaO₂ - partial pressure of oxygen, FiO₂ - Fraction of inspired oxygen. * Source: ICNARC report on COVID-19 in critical care 12 June 2020.

Demographics	NUHCC	National*
Age at admission (years) (N=109)		
Mean (SD)	56.5 (13.7)	58.7 (12.6)
Median (IQR)	58 (46, 68)	60 (51, 68)
Sex, n (%) (N=109)		
Female	37 (33.9)	2864 (29.3)
Male	72 (66.1)	6908 (70.7)
Currently or recently pregnant, n (% of females aged 16-49)		
Currently pregnant	0 (0)	25 (3.6)
Recently pregnant (within 6 weeks)	0 (0)	35 (5.1)
Not known to be pregnant	37 (100)	633 (91.3)
Ethnicity, n (%) (N=103)		
White	73 (70.9)	6008 (67.1)
Mixed	2 (1.9)	154 (1.7)
Asian	13 (12.6)	1339 (15.0)
Black	11 (10.7)	869 (9.7)
Other	4 (3.9)	583 (6.5)
Body mass index, n (%) (N=108)		
<18.5	1 (0.9)	60 (0.7)
18.5 - <25	30 (27.8)	2292 (25.3)
25 - <30	29 (26.9)	3158 (34.8)
30 - <40	36 (33.3)	2856 (31.5)
40+	12 (11.1)	710 (7.8)
Indicators of acute severity	NUHCC	National*
Mechanically ventilated within first 24h, n (%) (N=109)	68 (62.4)	5667 (60.9)
APACHE II Score		
Mean (SD)	15.3 (5.5)	14.9 (5.3)
Median (IQR)	15 (12, 19)	14 (11, 18)
PaO₂/FiO₂ ratio (kPa), median (IQR)	15.9 (11.7, 20.6)	15.7 (11.2, 22.0)
PaO₂/FiO₂ ratio, n (%) (N=108)		
≤ 13.3 kPa (≤ 100 mmHg)	45 (41.7)	3306 (37.2)
> 13.3 and ≤ 26.7 kPa (> 100 and ≤ 200 mmHg)	48 (44.4)	4267 (48.0)
> 26.7 kPa (> 200 mmHg)	15 (13.9)	1309 (14.7)

Table 2. Initial laboratory results for patients admitted to NUHCC with COVID-19. IQR - Inter-Quartile Range, No. - Number, Ref. Reference, PT - Prothrombin Time, APTT - Activated Partial Thromboplastin Time, CRP - C Reactive Protein, LDH - Lactate Dehydrogenase, AST - Aspartate Aminotransferase, ALT - Alanine Transaminase.

Initial Laboratory Results			
Parameter	Median (IQR)	No.	Ref. range
Leukocytes	8.98 (7.05, 11.21)	109	4 - 11 x 10 ⁹ /L
Lymphocytes	0.85 (0.64, 1.24)	109	1 - 4 x 10 ⁹ /L
Platelets	251 (193, 329)	109	150 - 450 x 10 ⁹ /L
Creatinine	82 (62, 108)	109	59 - 104 µmol/L
PT	11.4 (10.9, 11.8)	109	10 - 12 sec
APTT	24.9 (23.2, 27.9)	109	21 - 29 sec
Fibrinogen	6.01 (5.19, 7.22)	42	1.8 - 4 g/L
D-Dimer	1193 (711, 2070)	38	< 500 µg/L
CRP	222 (148, 293)	109	0- 10 mg/L
Lactate	1.2 (1, 1.9)	109	0.5 - 1.6 mmol/L
Ferritin	1384 (649, 2158)	56	25 - 350 µg/L
LDH	995 (769, 1355)	26	220 - 450 U/L
Troponin	18 (11.5, 132.3)	36	0 - 59 ng/L
Bilirubin	12 (8, 15)	109	0 - 21 µmol/L
AST	82 (61, 116)	71	0 - 35 U/L
ALT	43 (28, 63)	105	0 - 45 U/L

Table 3. Outcome and length of stay for patients admitted to NUHCC with COVID-19. NUHCC - Nottingham University Hospitals Critical Care, IQR - Inter-Quartile Range, SD - Standard Deviation.

*Source: ICNARC report on COVID-19 in critical care 12 June 2020.

Outcome and length of stay	NUHCC	National*
Outcome at end of critical care, n (%) (N=100)		
Discharged	74 (74.0)	5190 (58.4)
Died	26 (26.0)	3701 (41.6)
Outcome at end of hospital stay, n (%) (N=95)		
Discharged	68 (71.6)	
Died	27 (28.4)	
Outcome at end of critical care - Mechanically ventilated, n (%) (N=79)		
Survivors	57 (72.2)	
Non-survivors	22 (27.8)	
Outcome at end of hospital stay - Mechanically ventilated, n (%) (N=74)		
Discharged	52 (70.3)	
Died	22 (29.7)	
Length of stay in critical care (days), median (IQR) (N=100)		
Survivors	13 (7, 27)	11.5 (4, 25)
Non-Survivors	8 (4, 11)	9 (5, 15)
Survivors, Mean (SD)	17.3 (13.4)	
Non-Survivors, Mean (SD)	9.2 (6.1)	
Length of stay - ICU admission to hospital discharge (days), median (IQR) (N=95)		
Survivors	22 (14, 35)	
Non-Survivors	9 (4, 12)	
Survivors, Mean (SD)	24.6 (14.1)	
Non-Survivors, Mean (SD)	9.1 (6.2)	
Length of stay - Hospital admission to hospital discharge (days), median (IQR) (N=95)		
Survivors	24 (15, 36)	
Non-Survivors	11 (7, 18)	
Survivors, Mean (SD)	26.5 (14.4)	
Non-Survivors, Mean (SD)	11.1 (6.6)	
Duration of mechanical ventilation (days), median (IQR) (N=79)		
Survivors	19 (9, 27)	
Non-survivors	10 (5.8, 12.8)	
Survivors, Mean (SD)	19.6 (11.7)	
Non-Survivors, Mean (SD)	10.5 (6.3)	

Table 4. Summary data for first seven days of mechanical ventilation in patients admitted with COVID-19 to NUHCC. Updated ventilation guidance was implemented on 9th April. IQR - Inter-Quartile Range, SD - Standard Deviation, PEEP - Positive End Expiratory Pressure, DP - Driving Pressure, PAWP - Peak Airway Pressure, Vt - Tidal Volume (mL.Kg⁻¹ predicted body weight), MAWP - Mean Airway Pressure

Ventilation Data Summary						
Parameter	Overall		Before 9 th April		After 9 th April	
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)
PEEP (cmH₂O)	10 (8, 14)	10.0 (4.43)	12 (8, 14)	10.3 (4.6)	10 (8, 12)	9.3 (3.9)
DP (cmH₂O)	14 (11, 16)	14.3 (5.9)	14 (11, 16)	14.4 (5.8)	14 (11, 16)	14.1(6.2)
PAWP (cmH₂O)	25 (22, 28)	24.5 (5.3)	26 (22, 29)	24.9 (5.3)	24 (21, 27)	23.4 (5.1)
Vt (mL.Kg⁻¹)	7.1 (6, 8)	7.4 (1.8)	6.9 (6, 8)	7.3 (1.8)	7.4 (7, 9)	7.7 (1.8)
MAWP (cmH₂O)	17.7 (15, 20)	17.7 (3.6)	18.4 (16, 20)	18.1 (3.5)	16 (14, 19)	16.6 (3.7)

Table 5. NUHCC outcomes for those admitted with COVID-19 by patient characteristics in comparison to national data. NUHCC - Nottingham University Hospitals Critical Care, BMI- Body Mass Index. *Source: ICNARC report on COVID-19 in critical care 12 June 2020.

Outcomes by Patient Characteristics				
	NUHCC		National*	
	Discharged n (%)	Died n (%)	Discharged n (%)	Died n (%)
Age at admission (years)				
16-39	13 (81.3)	3 (18.8)	603 (84.5)	111 (15.5)
40-49	14 (87.5)	2 (12.5)	935 (77.9)	266 (22.1)
50-59	22 (81.5)	5 (18.5)	1582 (64.6)	868 (35.4)
60-69	13 (56.5)	10 (43.5)	1334 (51.1)	1275 (48.9)
70-79	10 (66.7)	5 (33.3)	628 (38.2)	1016 (61.8)
80+	2 (66.7)	1 (33.3)	107 (39.5)	164 (60.5)
Sex				
Female	27 (75)	9 (25)	1656 (63.5)	952 (36.5)
Male	47 (73.4)	17 (26.6)	3534 (56.3)	2747 (43.7)
BMI				
<25	18 (62.1)	11 (37.9)	1223 (57.7)	897 (42.3)
25 - <30	19 (76)	6 (24)	1621 (55.7)	1290 (44.3)
30 - <40	27 (81.8)	6 (18.2)	1629 (61.9)	1001 (38.1)
40+	8 (72.7)	3 (27.3)	413 (63.3)	239 (36.7)
Ethnicity				
White	50 (73.5)	18 (26.5)	3290 (59.5)	2243 (40.5)
Mixed	1 (50)	1 (50)	70 (53.0)	62 (47.0)
Asian	8 (80.0)	2 (20)	633 (52.7)	569 (47.3)
Black	7 (70)	3 (30)	425 (55.2)	345 (44.8)
Other	2 (50)	2 (50)	338 (65.0)	182 (35.0)

Figure 1. Incidence of thromboembolic events by week of admission, annotated with evolution of guidance for venous thromboembolism prophylaxis. LMWH - Low Molecular Weight Heparin, PE - Pulmonary Embolism, CVA - Cerebrovascular Accident.

Figure 2. Cohort flow of patients admitted with COVID-19 to NUHCC.

Figure 3. Number of admissions, mortality, APACHE II score and cumulative number of simultaneous confirmed COVID-19 cases in NUHCC by week, during evaluation period. ICU - Intensive Care Unit, APACHE II - Acute Physiology And Chronic Health Evaluation II.

Appendix

Appendix I. NUHCC Ventilation Strategy for COVID-19.
Appendix II - NUHCC COVID-19 Renal Management Strategy.

NUH Critical Care: COVID-19 Renal Management Strategy

This document has been produced to offer suggestions on the management of patients admitted to critical care with COVID-19 infection at Nottingham University Hospitals.

General considerations

- The COVID-19 pandemic presents an unprecedented challenge
- COVID-19 primarily causes an acute respiratory illness progressing to ARDS - but it is a multi-system disease

Specific considerations

- The reported rate of acute kidney injury in patients admitted to hospital with COVID-19 is between 3-9%ⁱ
- The exact mechanism is unclear
- 44% of patients were found to have proteinuria
- 26% had microscopic haematuria
- AKI is an independent risk factor for mortality in patients with COVID-19

Suggestions for the management of patients with COVID-19

Don't add insult to injury:

Review medication chart and omit drugs that are likely to increase the risk of AKI:

- ACE-inhibitors (-prils)
- Angiotensin-2 receptor blockers (-sartans)
- Non-steroidal anti-inflammatory drugs
- Potassium sparing diuretics (Spironolactone)
- Thiazide diuretics

Management of fluid balance

- Fluid overload in ARDS thought to cause increased mortality
- However - dehydration is a risk factor for AKI
- Below is a pragmatic decision aid offering suggestions on fluid management in COVID-19:

NUHCC: COVID-19 Renal Management Strategy
V2 | 1

Suggested strategies for avoiding fluid overload

Minimise fluid intake

- Avoid use of maintenance fluids
- Use concentrated enteral feed
- Use lowest volume of fluid in necessary infusions and drugs (such as glucose infusions for sliding scales)

Consider loop diuretics

- Patients passing more than 500mls of urine per day may benefit from loop diuretics
- Furosemide given intravenously is the preferred loop diuretic in critical care

Creatinine less than 99	Furosemide 40mg twice per day	If insufficient response increase to 80mg twice per day
Creatinine between 100 and 199	Furosemide 80mg twice per day	If insufficient response increase to 120mg twice per day
Creatinine greater than 200	Furosemide 120mg twice per day	If insufficient response seek ICU consultant advice. May be diuretic resistant

- Furosemide can be given by bolus or 24-hour infusion. Starting doses depend on renal function.
- Furosemide infusions are prescribed as 500mg made up to 50mls with 0.9% saline given at 1-2mls/hour
- Additional diuretics may be necessary to achieve the desired fluid balance.
- There are two enteral options - the choice of which will depend on the potassium level that day:
 - If K^+ is $>5\text{mmol/l}$ - add metolazone 5mg once per day via the nasogastric tube
 - If K^+ is $<5\text{mmol/l}$ - add amiloride 5mg twice per day via the nasogastric tube

Renal Replacement Therapy

Specific considerations

- It is likely the need for RRT will exceed the current capacity at NUHCC - placing a strain on the supply chain of consumables and machines
- Decisions to start and continue RRT must be made by the responsible ICU consultant and based on an ethical framework
- RRT should be considered when:

AKI 3 complicated by one or more of:

- Refractory hyperkalaemia $K^+ > 6.5\text{mmol/l}$
- Metabolic acidosis $\text{pH} < 7.1$
- Fluid overload refractory to diuretics
Defined as fluid overload in a patient on a rescue mode of ventilation not achieving a negative fluid balance on maximal diuretic therapy

Once the decision to start RRT has been made by the ICU consultant - the following steps should be considered:

Preference	Site	Length of line	Ideal tip position
First	Right Internal Jugular	15cm vascath	Tip in top of right atrium
Second	Femoral veins	20cm vascath	Inserted to the hub
Third	Left Internal Jugular	20cm vascath	Tip in top of right atrium
Fourth	Subclavian vein	15-20cm vascath	Tip in top of right atrium

- Ultrasound guided dialysis catheter placement by an appropriately skilled practitioner
- The catheter lumens should all aspirate and flush freely before securing the line
- Preferred catheter site as per table above:

The RRT prescription

During the COVID-19 pandemic we will use a default RRT prescription designed to maximise the longevity of the circuit and permit ultrafiltration. In non-COVID-19 patients, please seek advice from the ICU consultant.

Mode

- CVVHDF - continuous veno-venous haemodiafiltration will be the default mode

Dose

- The recommended effluent dose is 35mls/kg/hour
- The pre-dilution to post-dilution ratio should be 70:30
- The dialysate should be prescribed as 1000mls
- It may be reasonable to offer an intermittent therapy: 24 hours on - 24 hours off - if necessary
- A decision to discontinue the therapy should be made by the ICU consultant

Fluid balance

- Body fluid assessment should inform a fluid removal target
- It could be possible to aim for 1000ml - 2000ml negative balance over the course of a 12-hour treatment

Anticoagulation

- There are reports of clotting abnormalities in patients with COVID-19
- Anticoagulation will improve efficiency of treatment - but should be balanced against the risk of bleeding
- The default anticoagulant will be low molecular weight heparin (dalteparin see prescription chart)

Stopping RRT

- It is safe to pause RRT once pH >7.3 and K⁺ <5.5mmol/l
- It is difficult to be certain when a patient has regained independent renal function

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- Resolution of underlying cause and urine output of >1000mls per day are predictors of weaning from RRT

Troubleshooting

The most common cause for high access pressures and the loss of a circuit is poor vascular access placement.

The bedside nurse will manipulate the line into optimal position - if the problem persists consider:

- Lying the patient flat
- Is a fluid bolus appropriate? (this is unlikely to be the answer in fluid overloaded patients)
- If the patient is in the prone position - is it worth turning them supine?
- Provided solute clearance is acceptable ($K^t < 6\text{mmol/l}$) - increasing the pre and post-dilution ratio to 90:10 may be helpful - but will impair solute clearance
- Reducing the effluent rate to 25mls/kg/hour could be considered
- Consider starting or increasing the dose of anticoagulation
- A new line may be necessary

Note: Rising transmembrane pressures often herald imminent loss of circuit. Washing the circuit back before it clots will reduce the need for transfusions.

Failure to achieve adequate solute clearance may be a consequence of using higher pre and post dilution ratios.

Failure to clear potassium should lead the practitioner to consider:

- Excessive potassium release from virus induced rhabdomyolysis or compartment syndrome:
 - Check CK and examine patient for compartment syndrome
- Check the drug card and infusion chart for sources of potassium:
 - Enteral potassium, potassium acid phosphate infusions
- Medications such as co-trimoxazole, ACE-inhibitors, spironolactone or amiloride
- Ultimately the dose of RRT may need to be increased by:
 - Adjusting the pre and post-dilution ratio to 50:50
 - Increasing the treatment time
 - Increasing the effluent rate

Worsening pH

- Permissive hypercapnia will likely lead to a rise in the bicarbonate. RRT may lead to a fall in the serum bicarbonate and therefore a reduction in pH.
- If the clearance is acceptable then stopping dialysate is advised.
- An 8.4% sodium bicarbonate infusion at 25mls/hour may be necessary.

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¹ Naicker S et al. The novel Coronavirus 2019 epidemic and kidneys. *Kidney International*. 2020. DOI <https://doi.org/10.106/j.kint.2020.03.001>

Appendix III. Venous thromboembolism prophylaxis regimen updated on 9th April and 30th April. Guidance prior to COVID-19 was 40mg Enoxaparin once daily for those between 50 - 100kg, adjustments were made for creatinine clearance and extremes of weight.

Updated Guidance on 9th April: Enoxaparin doses for COVID-19 confirmed or suspected patients.

Renal Function	Weight			
	< 50kg	50 - 100kg	100 - 150kg	> 150kg
CrCl $\geq$ 30ml/min	20mg OD	40mg OD	40mg BD	60mg BD
CrCl 15 - 30ml/min	20mg OD	20mg OD	40mg OD	60mg OD
CrCl < 15ml/min	20mg OD			

Updated Guidance on 30th April: Enoxaparin doses for COVID-19 confirmed or suspected patients.

Renal Function	Weight			
	< 50kg	50 - 100kg	100 - 150kg	> 150kg
CrCl $\geq$ 30ml/min	20mg BD	40mg BD	60mg BD	80mg BD
CrCl 15 - 30ml/min	20mg OD	20mg OD	60mg OD	80mg OD
CrCl < 15ml/min	20mg OD			

Figures

Figure 1

Incidence of thromboembolic events by week of admission, annotated with evolution of guidance for venous thromboembolism prophylaxis. LMWH - Low Molecular Weight Heparin, PE - Pulmonary Embolism, CVA - Cerebrovascular Accident.

Figure 2

Cohort flow of patients admitted with COVID-19 to NUHCC.

Figure 3

Number of admissions, mortality, APACHE II score and cumulative number of simultaneous confirmed COVID-19 cases in NUHCC by week, during evaluation period. ICU - Intensive Care Unit, APACHE II - Acute Physiology And Chronic Health Evaluation II.