High Dependency Renal Unit (HDRU) for the management of COVID-19 in patients with severe acute or chronic kidney disease

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Abstract

Background: COVID-19 in patients on dialysis for acute or chronic kidney disease is associated with high mortality. We evaluated the effect of high dependency renal unit (HDRU) with nephrologists as primary care physicians for management of these patients.

Methods: This was an observational, cohort study conducted at a tertiary care teaching hospital in western India. Patients needing dialysis for COVID-19 associated Acute Kidney Injury (AKI-D) and patients with End-Stage-Renal-Disease (ESRD) hospitalized for COVID-19 were included in the study. After 2 months into the pandemic (28 March to 28 May 2020), HDRU was commissioned for management of these patients. With nephrologists as primary care physicians, the components of care included completion of care bundle focusing on key nephrology and COVID-19 related issues, checklist-based clinical monitoring, integration of multispecialty care, and training of nurses and doctors. Primary outcome of the study was in hospital mortality compared between pre-HDRU and HDRU cohorts. Secondary outcomes were- dialysis dependence in AKI-D, and predictors of death.

Results: 238 of 4254 (5.59%) patients with COVID-19 admitted from 28th March to 30th September had severe renal impairment (116 AKI-D and 122 ESRD). 145 (62%) had severe COVID-19. HDRU care was delivered from 28th May to 30th August. Kaplan-Meier survival analysis showed significant improvement in survival after implementation of HDRU [19 of 52 (36.5%) in pre-HDRU versus 35 of 160 (21.9%) in HDRU died, p=<0.01]. 44 (67.7%) AKI-D survivors were dialysis dependent at discharge. Breathlessness and altered mental status at presentation, development of shock during hospital stay and leukocytosis predicted mortality.

Conclusions: HDRU managed by nephrologists is a feasible and potentially effective approach to improve the outcomes of patients with COVID-19 and severe renal impairment.

Background

Patients with kidney diseases are prone to develop Coronavirus disease 2019 (COVID-19) and are more likely to get severe disease due to highly prevalent risk factors like advanced age, hypertension, diabetes, cardiovascular disease1–3. COVID-19 in patients with End Stage Renal Disease (ESRD) is associated with high mortality4. Similarly, several reports have highlighted high mortality due to COVID-19 in patients who develop acute kidney injury (AKI) and a significant number of AKI survivors remained on dialysis at the time of discharge from hospital5,6. Treatment of COVID-19 is largely supportive, and except dexamethasone, no therapy has shown survival benefit7.

Typically, hospitalized patients with severe renal impairment have multiple co-morbidities and medical issues like access dysfunction, blood stream infections, inadequate dialysis etc., which demand a close coordination among various specialties to avoid fragmentation of care. Patients with severe renal impairment because of AKI needing dialysis (AKI-D) and ESRD therefore represent one of the most vulnerable subsets of the hospitalized COVID-19 patients; strategies to improve outcomes in these

patients are urgently needed. We present here our experience of a high dependency renal unit (HDRU), primarily managed by nephrology team, which was commissioned to optimize the management of COVID-19 in patients receiving hemodialysis for acute or chronic kidney disease.

Methods

Our hospital is a 1800 bedded tertiary care public hospital in western India and is one of the largest public hospitals designated for hospitalization of patients with COVID-19. We started admitting patients with COVID-19 and kidney diseases from 28th March 2020. Consecutive patients with ESRD with COVID-19 and COVID-19 associated AKI-D were included for the study. The study was approved by Institutional Ethics Committee (IEC) of KEM hospital, Mumbai. Waiver of consent was obtained from the IEC (EC/OA/96/2020) and study was registered at Clinical Trial Registry of India (CTRI) (CTRI/2020/06/026152), date of registration-26/06/2020. Patients were evaluated by nephrology services within two hours of the hospitalization, and following data was obtained: demographic details, co-morbid conditions, vitals parameters -temperature, heart rate, respiratory rate, blood pressure in supine and sitting /standing position, assessment of hydration, and review of systems. Oxygen saturation on room air, arterial blood gas and chest x-ray was obtained at admission in all the patients. Severe COVID-19 illness was defined as oxygen saturation less than< 94% or any need of oxygen therapy. Acute Kidney Injury was defined by KDIGO criteria. Laboratory evaluation included complete blood count, renal and liver chemistries, C reactive protein, lactate dehydrogenase in all and d-dimer, interleukin 6, ferritin, in selected cases. High resolution computed tomography (HRCT) of chest was done in patients with severe disease or when felt necessary by treating physician. For the first two months, i.e. from 28th March 2020 to 28th May 2020, patients were admitted in a dedicated COVID-19 ward or intensive care unit (depending upon the severity of the illness) managed by primary care physicians. Staff and fellow nephrologists attended these patients once daily and decided about the need of dialysis initiation, dialysis discontinuation, and made suggestions about fluid therapy, diuretics, and drug dosing.

After auditing the outcomes of the patients and discussion with hospital administration, a dedicated 45 bedded COVID-19 High Dependency Renal Unit (HDRU), to be primarily managed by nephrology team, was commissioned on 28th May 2020. HDRU was staffed with 4 staff nephrologists, 3 nephrology fellows, and 10 fellows from other specialties, 14 nurses (including 4 dialysis nurses), 14 patient care assistants and 8 dialysis technicians. The 13 bedded COVID-19 hemodialysis unit was located next to the HDRU. A 6-bedded dialysis unit for all other non-COVID-19 patients was created in another area in the hospital. Fellows from other specialties received training sessions conducted by staff nephrologists (repeated every two weeks) which included overview of the management of patients with severe renal impairment, dialysis access care, acute dialysis procedure, monitoring during hemodialysis and acute complications related to dialysis. Staff and fellows from non-clinical specialties were included for managing logistics of the unit- provision of essential medical supplies and drugs, management of manpower, duty schedules of fellows, managing daily log and reporting of new cases, deaths, discharges,

facilitating transfers in and out of the unit and communication with patient's relatives by a daily telephonic call (Figure 1 and 2).

Upon admission to HDRU, patients were evaluated once every six hours: subjective assessment, focused clinical evaluation, vital parameters, oxygen saturation, blood glucose and arterial blood gas if needed. Three staff nephrologists evaluated patients 3 times daily focusing on vital parameters, volume status, need of fluids or diuretics, indicators of uremia and parameters concerning severity of COVID-19. Staff nephrologists evaluating these patients made decisions about the conservative management of AKI, need of starting or stopping dialysis, initiation of steroids, antivirals, other anti-inflammatory agents, prophylactic antibiotics and anticoagulant management (and mode of ventilation). Standard dose modifications for renal impairment were followed for all drugs and antibiotics. Inj. Remdesivir was administered as 200mg loading dose followed by 100mg once daily for 5 days (total 600mg) after written informed consent. Depending upon the severity of hypoxia, patients received oxygen (therapy) by nasal canula, venturi mask, non-rebreathing mask, high flow nasal cannula or non-invasive ventilation (NIV).

Checklist of the key clinical parameters to be monitored every sixth hourly was followed by staff nurses and duty doctors for patient monitoring. Staff nephrologists ensured that the crucial clinical issues (related and unrelated to COVID-19) were addressed as soon as possible after admission by completing the care bundle (Table 1). The six hourly HDRU duty rotations included fellows from different subspecialties like radiology, general surgery, psychiatry, dermatology, ophthalmology. The unit got priority consultation visits from cardiology, chest medicine, urology for cross specialty referral care (like bedside ultrasound of the urinary tract, IVC diameter, surgical debridement and dressings, patient counseling, 2D-echocardiography, urological evaluations). In charge nephrologists, who made the final decisions on the treatment ensured close coordination among various specialties.

Patients with worsening hypoxemia, hemodynamic instability, worsening AKI and severe organ dysfunction were triaged for more intensive monitoring, which included continuous monitoring of oxygen saturation, heart rate, rhythm, respiratory rate and blood pressure. Triaged patients were discussed daily on a telephonic conference call which followed the staff nephrologists' morning clinical rounds. This was attended by all staff nephrologists

Table 1: Components of High Dependency Renal Unit care

Checklist

Inform If

Heart rate	<60/min or >120/min
Respiratory rate	>30/min
Temperature	> 98 F
Oxygen saturation (sPO2)	<94%
Blood pressure, check for orthostasis, relative hypotension	<100mmHg or >160mmHg systolic or >20mmHg fall
Glasgow Coma Scale	Any change
Blood Glucose	< 70mg/dl or > 250mg/dl
Urine output	<1ml/kg/hour for 6 hrs
Bleeding	Any

Care Bundle

-

Volume and Blood pressure

Assess and correct volume depletion/volume overload

Identify relative hypotension and de-escalate antihypertensive therapy

Dialysis and Access

Ensure dialysis adequacy

Timely institution and withdrawal of dialysis in AKI-D

Maintaining functional dialysis access

Prompt recognition and treatment of CRBSI

Therapy related

	Screen for stress induced hypoxia in patients not on oxygen (6 min walk test, ABG analysis)
	Target O2 saturation >94%
	Identify patients for steroids, anticoagulation and remdesivir therapy
	Monitor and treat steroid induced hyperglycemia
Multispecialty care	
	Fellows from various clinical specialties
	Bedside specialty services (ultrasound, echocardiography, wound management etc)
	Daily Multidisciplinary Critical care committee meeting
	Death discussions
	Daily Teleconferencing among staff and fellow nephrologists
Training	Fellows from other clinical specialties about dialysis basics, monitoring, acute dialysis complications, dialysis access etc

and fellows to facilitate smooth communication across the duty shifts. Management decisions like initiation of anti-inflammatory and antiviral treatments (steroids, tocilizumab, and remdesivir) were also made during this call conference. In addition, all the patients with severe COVID-19 or with clinical worsening were discussed in an interdisciplinary critical care team meeting. Critical care committee consisted of a senior pulmonologist, anesthesiologist, cardiologist, diabetologist and intensivist, who met daily to discuss such patients where various therapy decisions were discussed and finalized. Patients needing intubation or invasive mechanical ventilation were transferred to intensive care units.

COVID-19 Hemodialysis Unit

A dedicated 13-bedded hemodialysis unit for dialysis of these patients was created adjacent to the HDRU. This was staffed with a nephrology fellow, one resident doctor from other clinical specialty, dialysis nurse, and dialysis technician round the clock. Intermittent hemodialysis (IHD) was continued for patients on maintenance hemodialysis and Slow Low Efficiency Dialysis (SLED) (QB 200, QD 300, duration 6 to 8 hours) was preferred for patients with hemodynamic instability. In patients with acute kidney injury, we followed the strategy of delayed initiation of dialysis- initiation only when clinically indicated for any of the following: refractory fluid overload, hyperkalemia, severe metabolic acidosis, alteration of the mental status attributable to uremia, or need of blood transfusion in the setting of oligo-anuria. Alternate daily dialysis was continued until recovery or discharge from the hospital. Patients during hemodialysis were monitored for vital parameters, continuous cardiac monitoring and pulse oximetry. Hemodialysis unit was equipped with facilities to provide high flow nasal oxygen, non-invasive and invasive ventilation in case of the deterioration in the oxygen saturation during dialysis treatment. Patients were considered for discharge after being asymptomatic for over 5 days, room air

oxygen saturation above 94% and no subjective sense of breathlessness and documentation of 2 negative RT-PCR swab tests done 5 days apart.

Statistical analysis was done using IBMâ SPSSâ Statistics software version 26. Quantitative variables were expressed as mean standard deviation (SD). Qualitative variables were expressed as numbers with percentage. Chi square or Fischer's exact test was used for categorical data. Independent samples t test was used for continuous data. Comparison of baseline, clinical and laboratory parameters between survivors and non-survivors was first done independently for AKI-D and ESRD groups, then for the combined group of all dialysis requiring patients. Comparison of these parameters was done for patients before and after implementation of HDRU. Primary outcome of the study was in-hospital mortality which was compared between pre and post HDRU cohorts. Causes of death were adjudicated by nephrologists treating the patients. Predictors of renal outcome (need of dialysis at discharge from hospital) in AKI-D group were analyzed. Depending on the nature of the variable, one or two-sided p value <0.05 was taken for statistical significance in univariate and multivariate analyses. Kaplan-Meier survival curves were generated for comparing pre and post HDRU survival, and comparison was done using log-rank test. A proportional monthly mortality rate was calculated by entering numerator as number of deaths in a given month and denominator as total number of patients cared for.

Results

Out of 4254 COVID-19 positive patients admitted to our hospital from 28th March 2020 to 30th September 2020, 238 (5.59%) patients had severe renal impairment (116 AKI-D and 122 ESRD). 52 of these patients were treated in COVID-19 medical wards or intensive care unit from 28th March to 28th May 2020 before the institution of HDRU. From 29th May to 31th August, 160 patients received treatment in HDRU. 26 patients were treated in a medical intensive care unit during this period as they needed mechanical ventilation within 48 hours of the hospital admission. (Figure 3). Baseline characteristics of the entire cohort, AKI-D and ESRD cohorts are summarized in Tables 2, 3 and 4 respectively.

Table 2: Characteristics for pre and post HDRU groups

Variable	Total (n= 234)	Pre-HDRU (n=48)	HDRU (n=160)	p-value
Demographic characters and co-morbidities				
Age (years)	50.4 (15.1)	45.3 (15.3)	51.5 (14.9)	0.012
Gender- Male (%)	152 (64.9%)	28 (58.3%)	103 (64.8%)	0.495
Hypertension (%)	180 (76.9%)	37 (77.1%)	127 (79.9%)	0.687
Diabetes mellitus (%)	96 (41.0%)	12 (25%)	74 (46.5%)	0.008
Cardiovascular Disease (%)	41 (17.5%)	9 (18.8%)	24 (15.1%)	0.510
Clinical features at admission				
Symptomatic at admission (%)	210 (89.7%)	37 (77.1%)	147 (92.5%)	0.007
Fever (%)	136 (58.1%)	28 (58.3%)	90 (56.6%)	0.869
Cough (%)	59 (25.2%)	13 (27.1%)	41 (25.8%)	0.853
Breathlessness (%)	132 (56.7%)	26 (54.2%)	89 (56.3%)	0.869
Vomiting (%)	44 (18.8%)	7 (14.6%)	33 (20.8%)	0.409
Diarrhoea (%)	30 (12.8%)	5 (10.4%)	20 (12.6%)	0.804
Sepsis at presentation (%)	48 (20.5%)	7 (14.6%)	31 (19.5%)	0.527
Shock at presentation (%)	19 (8.1%)	3 (6.3%)	11 (6.9%)	1.000
Altered mental status (%)	39 (16.7%)	9 (19.1%)	22 (13.8%)	0.362
Hypoxia at admission (%)	130 (55.6%)	21 (43.8%)	66 (41.5%)	0.868
Laboratory parameters at admission				
Hemoglobin (gm/dl)	8.6 (2.5)	8.7 (2.5)	8.5 (2.6)	0.680
Total Leukocyte Count (cells $x10^6$/L)	10571 (7116)	9505 (6680)	10285 (6755)	0.506
Platelets (cells $x10^9$/L)	206 (97.6)	186 (99.9)	206 (83.8)	0.210
Blood Urea Nitrogen (mg/dl)	72.7 (48.3)	63.7 (25.4)	74.3 (51.5)	0.076
Creatinine (mg/dl)	9.7 (5.4)	11.3 (5.4)	9.6 (5.6)	0.065
Sodium (meq/L)	131.7 (6.4)	132.1 (5.7)	131.1 (6.4)	0.392
Potassium (meq/L)	4.9 (1.1)	5.2 (1.0)	4.9 (1.1)	0.073
SGOT (IU/L)	37.8 (27.5)	36.1 (19.7)	36.9 (27.5)	0.858
SGPT (IU/L)	34.5 (68.2)	22.6 (15.8)	37.1 (77.6)	0.260

Treatment and course of stay				
Inotrope use (%)	57 (24.4%)	12 (25%)	36 (22.6%)	0.702
Requirement of blood transfusions (%)	93 (40.4%)	18 (37.5%)	68 (43.3%)	0.508
Steroids (%)	142 (61.5%)	28 (58.3%)	94 (59.9%)	0.868
Remdesivir (%)	45 (19.2%)	0 (0%)	35 (22%)	0.000
Heparin (%)	78 (33.8%)	16 (33.3%)	50 (31.8%)	0.861
HCQS (%)	111 (48.1%)	44 (91.7%)	62 (39.5%)	0.000
COVID Stage- Mild (%)	89 (38.0%)	17 (35.4%)	68 (42.5%)	0.000
-Severe (%)	145 (62.0%)	31 (64.6%)	92 (57.5%)	
Duration of O2 requirement (days)	5.3 (7.1)	3.8 (4.2)	5.7 (7.9)	0.029

Mean age of the study population was 50.4 years and 152 (64.9%) were men. Hypertension, diabetes and cardiovascular disease were present in 180 (76.9%), 96 (41.0%) and 41 (17.5%) respectively. Common presenting clinical features included fever 136 (58.1%), breathlessness 132 (56.7%), cough 59 (25.2%), vomiting 44 (18.8%), and diarrhoea 30 (12.8%). Severe COVID-19 was present in 145 (62%) of 234 patients during the course of hospitalization. All the patients were treated with IHD or SLED (except 1 patient who was treated with acute peritoneal dialysis).

Table 3: Characteristics and comparison between survivors and non-survivors in patients with AKI-D

Variable	Total (n=116)	Survived (n=65)	Expired (n=51)	p-value
Demographic characters and co-morbidities				
Age (years)	52.6 (14.8)	50.1 (14.6)	55.8 (14.5)	0.040
Sex- Male (%)	74 (63.8%)	39 (60%)	35 (68.6%)	0.437
Hypertension (%)	76 (65.5%)	44 (67.7%)	32 (62.7%)	0.694
Diabetes Mellitus (%)	55 (47.4%)	26 (40%)	29 (56.8%)	0.053
Chronic Kidney Disease (%)	81 (69.8%)	48 (73.8%)	33 (64.7%)	0.195
Cerebrovascular disease (%)	10 (8.6%)	3 (4.6%)	7 (13.7%)	0.083
Coronary Artery Disease (%)	10 (8.6%)	3 (4.6%)	7 (13.7%)	0.083
Clinical features at admission				
Symptoms present at admission (%)	111 (95.7%)	60 (92.3%)	51 (100%)	0.051
Duration of symptoms (days)	6.93 (7.0)	7.10 (7.7)	6.75 (6.1)	0.792
Fever (%)	64 (55.2%)	33 (50.8%)	31 (60.8%)	0.187
Cough (%)	23 (19.8%)	13 (20%)	10 (19.6%)	0.574
Breathlessness (%)	68 (58.6%)	30 (46.9%)	38 (74.5%)	0.002
Vomiting (%)	27 (23.3%)	16 (24.6%)	11 (21.6%)	0.437
Diarrhoea (%)	17 (14.7%)	8 (12.3%)	9 (17.6%)	0.292
Heart Rate (beats/min)	92.18 (15.77)	90.72 (15.94)	94.04 (15.52)	0.263
Systolic Blood Pressure (mmHg)	130.32 (23.98)	129.12 (21.67)	131.84 (26.79)	0.547
Diastolic Blood Pressure (mmHg)	80.59 (13.00)	80.40 (12.67)	80.84 (13.55)	0.856

Admission sPO_2[#] (sPO_2%)	90.85 (12.46)	94.63 (6.78)	86.04 (16.01)	0.001
Hypoxia at admission (%)	55 (47.4%)	21 (32.3%)	34 (66.67%)	0.000
Sepsis at presentation (%)	30 (25.9%)	14 (21.5%)	16 (31.4%)	0.162
Shock at presentation (%)	10 (8.6%)	6 (9.2%)	4 (7.8%)	0.532
Oliguria at presentation (%)	55 (47.4%)	27 (41.5%)	28 (54.9%)	0.107
Altered mental status (%)	31 (26.7%)	7 (10.8%)	24 (47.1%)	0.000
Laboratory parameters at admission				
Hemoglobin (mmol/L)	5.37 (1.68)	5.14 (1.71)	5.65 (1.61)	0.109
Total Leukocyte Count (cells $x10^6$/L)	12010 (8366)	10116 (7435)	14311 (8916)	0.009
Platelets (cells $x10^9$/L)	214.50 (107.10)	201.16 (92.47)	230.71 (121.55)	0.145
Blood Urea Nitrogen (mmol/L)	30.7 (20.1)	28.9 (16.7)	33.0 (24.0)	0.341
Creatinine (µmol/L)	872.7 (571.2)	969.1 (658.7)	752.5 (411.2)	0.043
Sodium (mmol/L)	131.49 (7.03)	131.45 (7.10)	131.54 (7.02)	0.944
Potassium (mmol/L)	4.89 (1.09)	4.76 (1.03)	5.05 (1.16)	0.165
AST (IU/L)	36.82 (27.20)	29.92 (17.86)	46.24 (34.04)	0.004
ALT (IU/L)	32.02 (38.02)	26.92 (33.46)	38.78 (42.78)	0.111
Treatment and course of stay				
Inotrope use (%)	40 (34.5%)	10 (15.4%)	30 (58.8%)	0.000
Requirement of PCV transfusions (%)	51 (43.9%)	33 (50.7%)	18 (35.3%)	0.069
Steroids (%)	73 (62.9%)	35 (53.85%)	38 (74.51%)	0.033

Remdesivir (%)	29 (27.1%)	13 (21.3%)	16 (34.8%)	0.092
Heparin (%)	41 (35.34%)	17 (26.15%)	24 (47.06%)	0.031
HCQS (%)	50 (43.1%)	26 (40%)	24 (47.06%)	0.457
Severe COVID-19	79 (68.1%)	32 (40.5%)	47 (59.5%)	0.000
Hospital stay (days)	16.67 (12.77)	20.86 (12.33)	11.41 (11.38)	0.000
Renal survival (dialysis independence at discharge)				
Variable	Total (n= 65)	Dialysis independent at discharge (n= 21)	Discharged on dialysis (n= 44)	P value
Hypertension (%)	44 (67.7%)	10 (22.7%)	34 (77.3%)	0.019
Diabetes Mellitus (%)	26 (40.0%)	10 (22.7%)	16 (36.4%)	0.275
Chronic Kidney Disease (%)	49 (75.4%)	11 (22.5%)	38 (77.6%)	0.004
Oliguria (%)	28 (43.1%)	10 (47.6%)	18 (40.9%)	0.403
Severe COVID-19 (%)	24 (36.9%)	10 (47.6%)	14 (31.8%)	0.168

Footnotes:

#Best maintained sPO2 at admission

Shock at presentation, shock during hospital stay and sepsis was present in 19 (8.1%), 57 (24.4%) and 48 (20.5%) patients respectively. 145 (62%) of all patients required oxygen supplementation at admission or during hospital stay. Oxygen requirements at admission were nasal prongs- 1 (0.43%), face mask- 45 (19.2%), non-rebreathing mask- 45 (19.2%), non-invasive mechanical ventilation- 9 (3.8%) and invasive mechanical ventilation- 4 (1.7%). 24 (20.6%) and 17 (14.4%) patients in AKI-D and ESRD group developed need of respiratory support after admission. 36 (31%) patients with AKI-D and 16 (13.5%) patients with ESRD needed mechanical ventilation during the stay (Supplementary Table 1). 3 of 122 (2.5%) patients in ESRD group had documented episode of Acute Coronary Syndrome (ACS) during ward stay, all recovered

with medical management. Steroids, hydroxychloroquine and remdesivir were given in 142 (61.5%), 111 (46.6%) and 45 (19.2%) patients respectively.

Table 4: Characteristics and comparison between survivors and non-survivors in patients with ESRD

Variable	Total (n=118)	Survived (n=93)	Expired (n=25)	p-value
Demographic characters and co-morbidities				
Age (years)	48.2 (15.2)	46.8 (15.7)	53.4 (12.3)	0.048
Sex -Male (%)	78 (66.1%)	59 (63.4%)	19 (76%)	0.341
Hypertension (%)	104 (88.1%)	82 (88.2%)	22 (88.0%)	1.000
Diabetes Mellitus (%)	41 (34.7%)	31 (33.3%)	10 (40%)	0.346
Cerebro-vascular disease (%)	6 (5.1%)	4 (4.3%)	2 (8.0%)	0.488
Coronary Artery Disease (%)	10 (8.5%)	3 (3.2%)	7 (2.8%)	0.043
Dialysis characteristics				
Dialysis vintage (months)	30.8 (38.2)	27.6(33.9)	42.5(50.6)	0.105
Dialysis vintage <1 year >1 year	49(48.5%) 52(51.5%)	40(51.2%) 38(48.7%)	9(39.1) 14(60.9%)	0.349
Arterio-venous fistula (%)	73 (64.6%)	59 (67.0%)	14 (56%)	0.329
Temporary catheter (%)	24 (21.2%)	16 (18.2%)	8 (32%)	
Tunnelled Cuffed Catheter (%)	16 (14.2%)	13 (14.8%)	3 (12%)	
Freq of HD- 3/week*	82 (74.5%)	67 (77.9%)	15 (62.5%)	0.183
Missing HD sessions > 3days	35 (29.7%)	24 (26.7%)	11 (45.8%)	0.070
Clinical features at admission				
Symptoms present at admission (%)	99 (83.9%)	74 (79.6%)	25 (100%)	0.007
Duration of symptoms (days)	4.45 (4.2)	4.3 (4.4)	4.9 (3.6)	0.569
Fever (%)	72 (61.0%)	58 (62.4%)	14 (56%)	0.361
Cough (%)	36 (30.5%)	24 (25.8%)	12 (48.0%)	0.031
Breathlessness (%)	64 (54.2%)	45 (48.4%)	19 (76.0%)	0.012
Vomiting (%)	17 (14.4%)	13 (13.9%)	4 (16%)	0.508
Diarrhoea (%)	13 (9.6%)	9 (9.7%)	4 (16%)	0.283
Heart Rate (beats/min)	91.9 (11.7)	91.92 (12.02)	91.76 (11.42)	0.952

Systolic Blood Pressure (mmHg)	132.3 (25.2)	135.18 (24.70)	121.80 (26.58)	0.020
Diastolic Blood Pressure (mmHg)	81.8 (13.9)	83.49 (13.47)	75.00 (14.36)	0.007
Admission sPO_2# (sPO_2%)	92.4 (11.5)	94.18 (6.79)	90.00 (9.26)	0.014
Hypoxia at admission (%)	49 (42.9%)	31 (34.8%)	18 (72%)	0.001
Sepsis at presentation (%)	18 (15.3%)	11 (11.8%)	7 (28%)	0.052
Shock at presentation (%)	9 (7.6%)	5 (5.4%)	4 (16%)	0.094
Altered mental status (%)	8 (67.8%)	3 (3.2%)	5 (20%)	0.011
Laboratory parameters at admission				
Hemoglobin (mmol/L)	5.34 (1.43)	5.22 (1.41)	5.65 (1.58)	0.195
Total Leukocyte Count (cells x10^6/L)	9108 (5207)	8503 (4721)	11629 (6270)	0.009
Platelets (cells x10^9/L)	196 (86.5)	200.61 (93.97)	201.16 (87.36)	0.981
Blood Urea Nitrogen (mg/dl)	60.1 (34.9)	56.55 (33.20)	72.48 (39.88)	0.059
Creatinine (mg/dl)	9.6 (4.2)	9.29 (10.56)	10.56 (6.24)	0.368
Sodium (mmol/L)	132.1 (5.6)	131.7 (5.7)	133.1 (5.1)	0.343
Potassium (mmol/L)	5.0 (1.0)	5.1 (1.1)	4.9 (1.0)	0.657
AST (IU/L)	38.7 (27.8)	36.66 (28.90)	47.76 (24.84)	0.110
ALT (IU/L)	37.1 (88.8)	40.55 (101.01)	27.20 (15.57)	0.549
Treatment and course of stay				
Inotrope use (%)	17 (14.4%)	6 (6.5%)	11 (44%)	0.000
Sepsis during stay (%)	22 (19.3%)	14 (15.7%)	8 (32.0%)	0.066
Requirement of PCV transfusions (%)	42 (36.8%)	36 (40.0%)	6 (25%)	0.132
Steroids (%)	69 (60.0%)	51 (56.0%)	18 (75%)	0.106
Remdesivir (%)	16 (13.6%)	10 (10.7%)	5 (23.8%)	0.103
Heparin (%)	37 (32.17%)	23 (25.3%)	14 (58.33%)	0.003
HCQS (%)	61 (53.0%)	46 (50.5%)	15 (62.5%)	0.361
Severe COVID-19 (%)	66 (55.9%)	43 (65.2%)	23 (34.8%)	0.000
Hospital stay (days)	16.9 (12.2)	18.6 (10.5)	11.6 (16.2)	0.013

Footnotes:

*Frequency of maintenance hemodialysis sessions was <3/week in the others

#Best maintained sPO2 at admission

Outcomes

76 (31.9%) of 238 patients died [AKI-D- 51 (43.9%), ESRD- 25 (21.2%)]. 19 (36.5%) and 35 (21.9%) patients died in the pre and post HDRU groups. Comparison of baseline, clinical and laboratory features of the patients treated before and after institution of HDRU are summarized in Table 2. Patients cared for in HDRU were older (51.5 versus 45.3 years, p=0.012), were more likely to be diabetic (46.5% versus 25%, p=0.008) and be symptomatic at admission (92.5% versus 77.1%). They also needed longer oxygen therapy (5.7 days versus 3.8 days, p=0.029). Kaplan-Meier survival analysis showed that introduction of HDRU led to significant decrease in mortality in overall cohort (Figure 4) and individually in AKI-D (Supplementary Figure 1), and tending towards significance in ESRD group (Supplementary Figure 2). The proportionate monthly mortality for patients is indicated in Supplementary Figure 3. Of 65 patients of AKI-D survivors, while 44 (67.7%) patients remained dialysis dependent. Pre-existing hypertension (77.3% versus 22.7%, p=0.019) and CKD (77.6% versus 22.5%, p=0.004) were associated with dialysis dependence.

Predictors of survival

Among AKI-D cohort, hospitalized patients who expired were more likely to be older (55.8 versus 50.1 years, p=0.040), have diabetes (56.8% versus 40%, p=0.053), and cardiovascular disease (27.5% versus 9.2%, p=0.013). They were more likely to present with breathlessness (74.5% versus 46.9%, p=0.002), hypoxia (66.7% versus 32.3%, p=0.000), altered mental status (47.1% versus 10.8%, p=0.000), leukocytosis (14,311 x 10^6/L versus 10,116 x 10^6/L, p=0.009), elevated aspartate transaminase (46.24 versus 29.92, p=0.004), and were more likely to need inotropic support (58.8% versus 15.4%, p=0.000).

Expired patients in ESRD group, were more likely to be older (53.4 versus 46.8 years, p=0.048), have cardiovascular disease (32% versus 13.9%, p=0.041), have breathlessness (76% versus 48.4%, p=0.012) and cough (48% versus 25.8%, p=0.031) at admission. They also had lower systolic (122mmHg versus 135mmHg, p=0.020) and diastolic (75mmHg versus 84 mmHg, p=0.007) blood pressures, hypoxia (72% versus 34.8%, p=0.001), sepsis (28% versus 11.8%, p=0.052), and altered mental status at presentation (20% versus 3.2%, p=0.011), leukocytosis (11,629 x 10^6/L versus 8,503 x 10^6/L, p=0.009), shock during stay (44% versus 6.5%, p=0.000) as compared to survivors. Severe COVID-19 infection was a risk factor for death in both cohorts in univariate analysis (AKI-D- 82.35% versus 38.46%, p=0.000, ESRD- 84% versus 38.1%, p=0.001).

In stepwise forward conditional regression analysis for the entire cohort (Supplementary Table 2), breathlessness and altered mental status at presentation, shock during hospital stay and leukocytosis were independent predictors of death. For AKI-D cohort, presence of shock at presentation or developing during stay and altered mental status at presentation were the only features predicting mortality. In patients with ESRD, shock at presentation or developing during stay, altered mental status, severe COVID-19 illness predicted mortality.

Non-COVID-19 issues at admission and cause specific mortality

49 of 238 patients (20.6%) had significant medical issues apart from COVID-19 at the time of admission, which included tropical infections and sepsis (urinary or dialysis access related) in 28 patients and issues due to underlying medical condition in 21 patients. In ESRD cohort, 35 of 118 (29.6%) had an inter-dialytic interval of >3 days due to missed dialysis session prior to admission. 14 (11.9%) had complications related to hemodialysis access at admission. In 25 of 76 (32.9%) patients who died, cause of death was not directly related to COVID-19 acute respiratory distress syndrome (ARDS). Causes of death in these patients were sepsis- 10, cardiac – 7, intra-cerebral bleeding- 6, malignancy- 1 and complications of uremia-1. In patients on HCQS, we did not encounter any cardiac arrhythmias or sudden cardiac deaths, though 7 patients showed QTc prolongation (480 msec), which necessitated stopping of HCQS.

Discussion

Our data suggests that COVID-19 in patients with severe acute or chronic kidney disease needing dialysis (AKI-D and ESRD) is associated with significant mortality and morbidity. It is feasible for a dedicated nephrology team to deliver high dependency care, implementation of which can lead to significant improvement in the survival. Presence of leukocytosis, breathlessness, altered mental status at presentation and development of shock during hospital stay were independent predictors of death. In patients with AKI, survivors had a high risk of dialysis dependence which was significantly associated with presence of CKD and hypertension at baseline.

To our knowledge, this is the first report of the nephrologists as primary care physician for the management of COVID-19 and care in HDRU set-up leading to improvement in survival. Key components of HDRU i.e. checklist based close clinical monitoring, care bundle approach focusing on key clinical issues and integration of multispecialty care by primary care physician-nephrologists most likely underlie the observed benefits of HDRU. Sudden and unexpected clinical deterioration is not uncommon in patients with COVID-19[8]. In a report from Italy, patient with ESRD and COVID-19 assigned to outpatient management based upon initial evaluation, experienced late clinical deterioration and associated mortality.[9] 41 of 234 (17.5%) patients in our cohort were not hypoxic at admission and developed the need of respiratory support during hospitalization; highlighting the need of close monitoring. Checklist of the key clinical parameters enabled us to quickly identify such patients and triage them for closer

monitoring. Use of checklists for the management of critically ill patients can reduce the errors of omission and potentially improve the outcomes[10] and their use by fellows and nurses working in six hourly rotations simplified the relatively complex process of caring for hospitalized patients on dialysis. Bundle care approach which focused on prompt optimization of hemodynamics, dialysis adequacy, dialysis access issues and therapies of COVID-19 ensured that key clinical needs were addressed as soon as possible after admission.

20.6% of the patients had major medical issues apart from COVID-19 at admission and 32.9% the deaths were not directly related to COVID-19 ARDS. This makes strong case for involvement of nephrologists as the primary care physician for the management of these patients. For instance, relative hypotension, which in critically ill patients is associated with Major Adverse Kidney Events (MAKE)[11], was observed more often in patients who died. Staff nephrologists ensured that this was promptly identified, and such patients were monitored closely for further deterioration.

Our cohort of AKI-D patients had a high rate of dialysis dependence at discharge, which could possibly be due to high prevalence of CKD at baseline; however, this could also be due to higher survival and discharge rates in our cohort as compared to the reported literature. Large number of patients needed transfer to chronic dialysis, and this process-involving counseling of patients and families, chronic dialysis access and plan of follow up care was facilitated in the presence of nephrologists as primary care physicians. High mortality (54.5%) in the first year (22.5% in the first month) early after dialysis initiation has been reported in elderly patients with morbidities[12], highlighting the importance of period of 'transition' in the care where nephrologists can play crucial role.

Hospitalized patients with both CKD and COVID-19 typically have multiple co-morbidities[13,14] which potentially lead to fragmentation of the care and can contribute to adverse clinical outcomes. Coordination among multiple specialties can be challenging especially during the pandemic time, but is vital for the management of the patients with multi morbidities. Daily conference and critical care committee meeting facilitated direct communication within the team and across the specialties, thus preventing fragmentation of care.

Higher risk of death reported in men with COVID-19 in general population,[14,15] has not been observed in our study. Shock during the hospital stay was probably related to severe systemic inflammation at presentation and development of sepsis, which contributed to mortality. This finding is further supported by association of leukocytosis with mortality. While bacterial sepsis in not a common feature of COVID-19, reported as 3.8% in a series[16], 21 (9%) of our patients had sepsis at presentation. Patients with CKD and ESRD are 100-300 times prone to sepsis associated mortality[17]. Altered mental status at presentation was associated with mortality, indicating multisystem involvement in severe COVID-19, severe uremia due to missed regular dialysis sessions or sepsis itself. 35 (28.5%) patients missed their scheduled dialysis sessions after diagnosis of COVID-19 as indicated by long interval of >3 days from their last dialysis session. This highlights the importance of rapid evaluation and management of sepsis (with antimicrobials or access removal) and optimization of dialysis dose in these patients.

Our study has limitations. Being an observational study, definite conclusions about survival benefits of HDRU can't be made. Imbalances in the baseline characteristics of the patients were noted in the pre and post HDRU cohorts: post HDRU cohort patients were older, more likely to be diabetic, present with symptoms, need oxygen for longer duration, were less likely to receive HCQS and more likely to receive remdesivir. Therapy of COVID-19 is evolving and learning curve issues in the management of disease early in the course might underlie the observed higher mortality in pre-HDRU cohort. Treatment protocols were modified with time as per the available evidence (fewer patients receiving HCQS, more patients getting remdesivir in HDRU). However, these imbalances are unlikely to explain the marked decrease in the mortality after HDRU as no single therapy has shown to decrease mortality so far. Patients receiving HCQS were monitored regularly for QT interval and arrhythmias, and sudden cardiac deaths were not observed in these patients. Pre HDRU cohort in our study was small, however, our post-HDRU cohort had far lower mortality rate in AKI-D than reported in a large study (43.9% vs 64%).[18] Similarly, post-HDRU ESRD cohort mortality rate is lower than those reported in India[19] (37%) and elsewhere (31%[4], 27.3%[20]). These observations support the beneficial effect of HDRU on outcomes.

In conclusion, it is feasible for nephrologists to deliver high dependency renal care. Pandemics like COVID-19 typically result in disruption of routine health care, pressurize existing resources and cause fragmentation of medical care, all of which contribute to overall morbidity and mortality. Our experience highlights the potential utility of HDRU in decreasing mortality of COVID-19 in one of the most vulnerable patient populations. As the COVID-19 pandemic continues despite mass vaccination programs and global measures to control its spread, we believe our experience will benefit many hospitals, especially in resource limited settings. Further evaluation of this approach is needed.

Declarations

Ethics approval and consent to participate: Study was approved by Institutional Ethics Committee (EC/OA/96/2020). All study procedures were conducted in accordance with the guidelines of IEC and declarations of Helsinki.

Consent for publication: yes

Availability of data and materials: Raw data obtained through this observational study is available on Mendeley Data. DOI:10.17632/k4shbbtyhr.1

Competing interests: none

Funding: none, all the treatment and evaluations were supported by the municipal corporation with no cost to the patients

Disclosures: We declare that we don't have any conflict of interest relevant to the subject of the article.

Author contributions: CG, TM, SD, SB evaluated the patients upon admission and informed to AP, ST DB, and TJ. DB, TJ and AP made final decisions about evaluations and treatments. ST and TJ designed the study, monitored data collection, adjudicated causes of death and wrote first draft. DB trained the fellows, DB and TJ supervised overall activities of the HDRU, AP, SP, AP supervised activities of the hemodialysis unit, AP monitored bedside dialysis activities. NS, AK, SD, SB, TM, CG collected the first evaluation data.

AK, CG collected data during ward stay. PJ did statistical analysis. ST wrote initial draft and TJ wrote the final draft.

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Figures

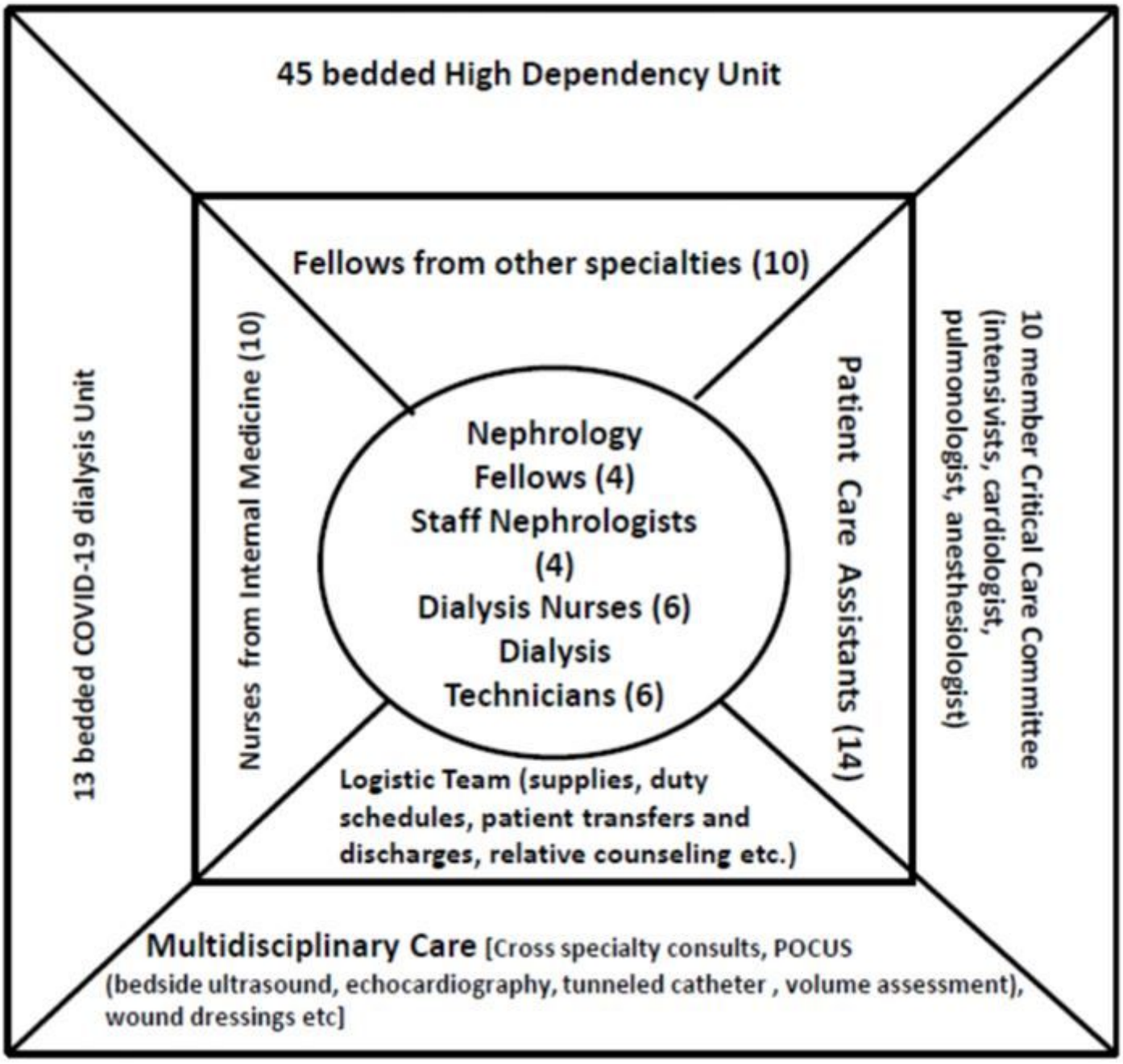


Figure 1

Structure of High Dependency Renal Unit

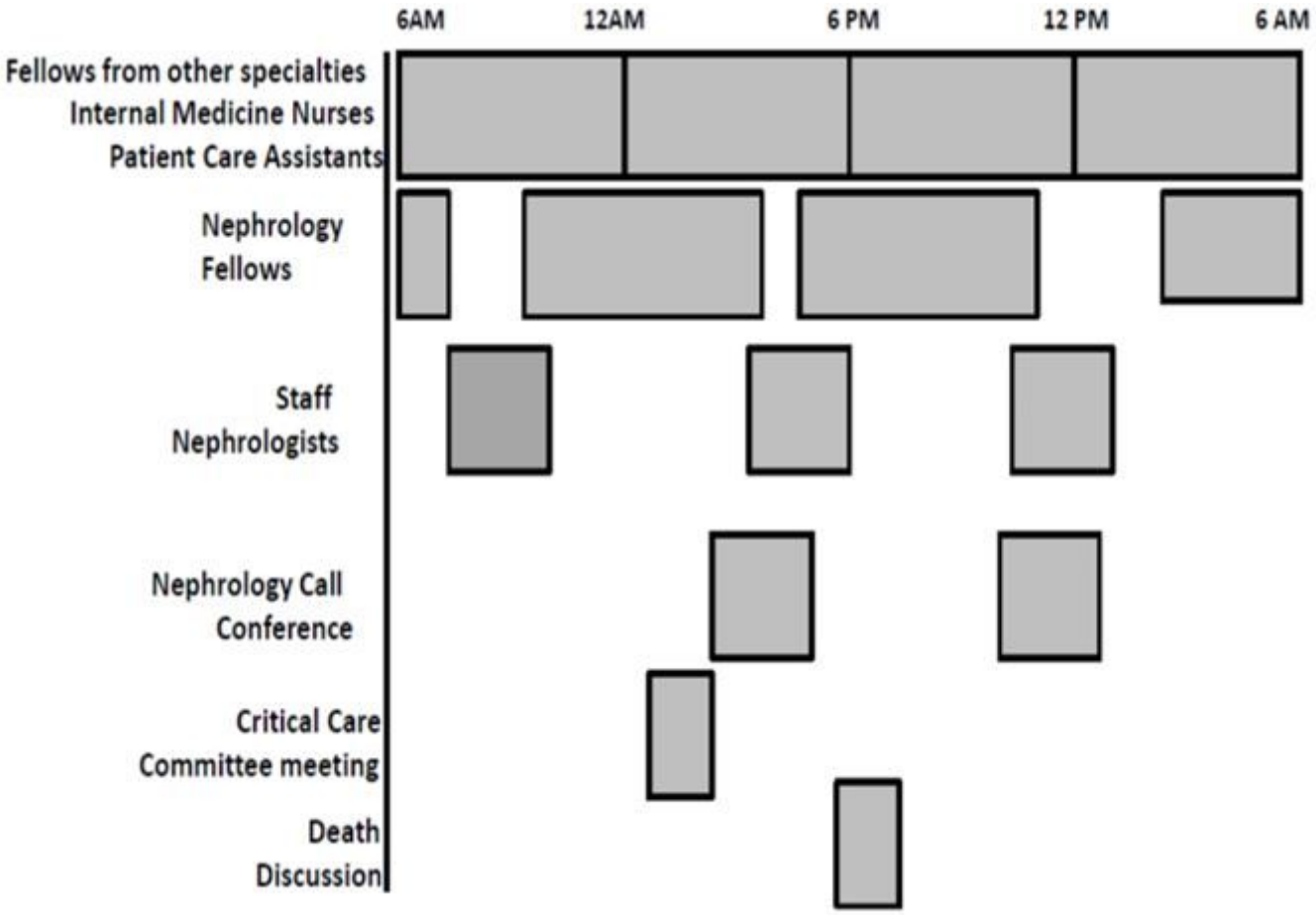


Figure 2

Functioning of High Dependency Renal Unit

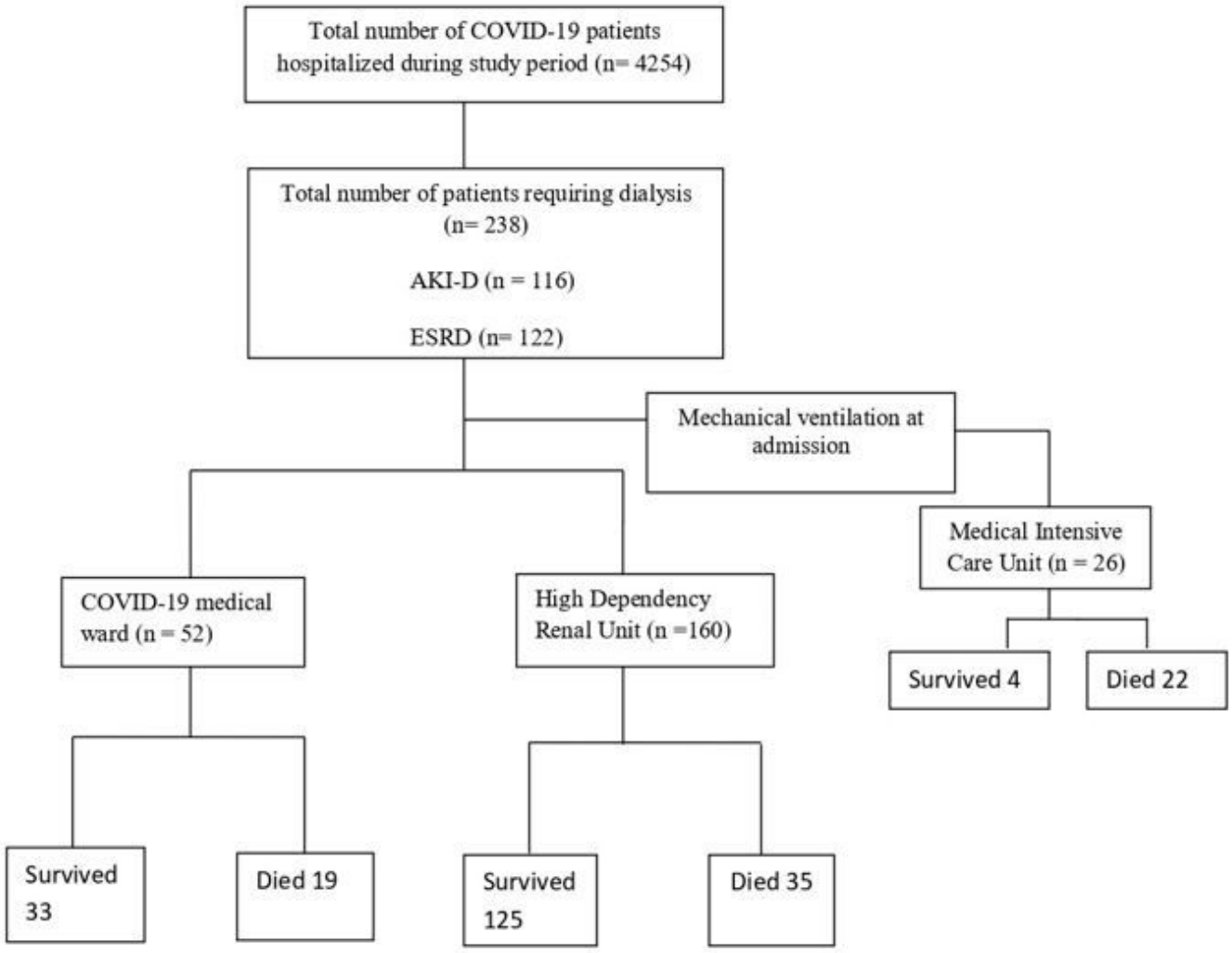
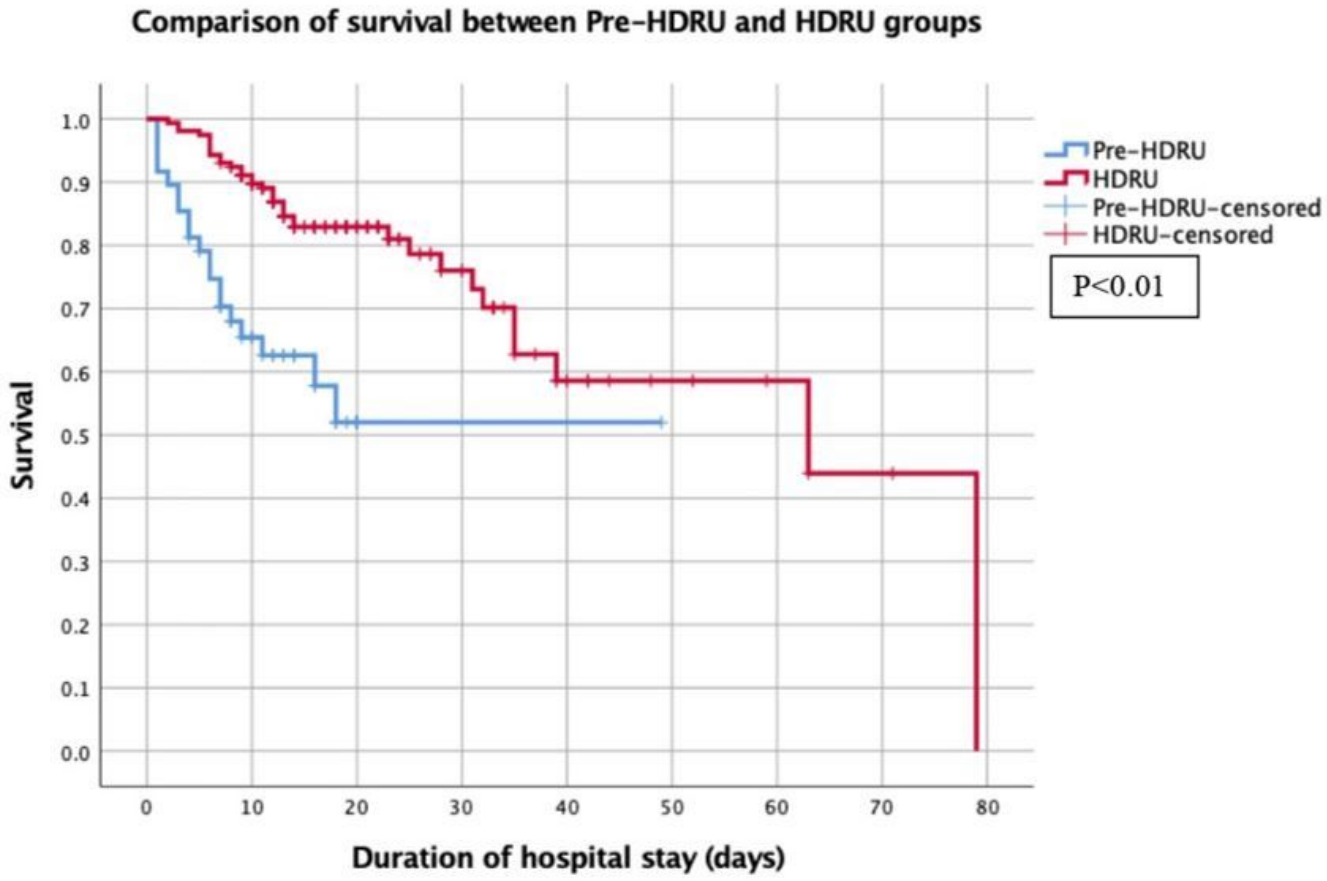


Figure 3

Study Flow Chart. Analysis of predictors of mortality (n = 234, AKI-D- 116, ESRD- 118), excluding 4 patients in ESRD cohort with missing data (transferred- 3, missing records-1)



HDRU	158	143	134	131	126	126	125	125	124
Pre-HDRU	52	36	33	33	-	-	-	-	-

Figure 4

Kaplan Meier survival curves for pre-HDRU and HDRU groups

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1Hypoxiamanagement.docx
- SupplementaryFigure1KMAKID.docx
- SupplementaryFigure2KMESRD.docx
- SupplementaryFigure3Proportionalmortality.docx
- SupplementaryTable2Predictorsofsurvival.docx