Timing of CRRT Initiation Based on AKI Diagnosis in ECMO: A Retrospective Study to Investigate Renal Recovery

Diane Braxmeyer

Oregon Health and Science University

Abstract

Background: Patients requiring extracorporeal membrane oxygenation (ECMO) support often experience acute kidney injury (AKI) as a result of their inciting illness and are at high risk for progression to chronic kidney disease (CKD) and hemodialysis dependence. Continuous renal replacement therapy (CRRT) supports renal function during AKI until renal recovery can occur, yet current research is unclear if CRRT can prevent progression to CKD. A retrospective study was conducted to explore the association of early CRRT implementation and renal recovery in patients requiring ECMO support.

Methods: A retrospective chart review was conducted for all patients ≥ 18 years old admitted to a single quaternary facility between January 2016 through December 2019 who received ECMO support and concurrent CRRT and survived to discharge. A total of 56 patients were included in the study. The independent variable was defined as time lapse between AKI diagnosis and initiation of CRRT. AKI was defined as an increase in serum creatinine (sCr) by ≥ 0.3 mg/dl within 48 hours, increase in sCr 1.5x that of baseline within 7 days, or a urine output of ≤ 0.5 ml/kg/hr for six hours. The dependent variable of renal recovery was defined as sCr upon discharge from the hospital and expressed as estimated glomerular filtration rate (eGFR). Primary outcome measure was eGFR at time of hospital discharge. Secondary outcome measures included criterion met for AKI diagnosis, time to initiation of CRRT once AKI diagnosis made, hemodialysis dependence at discharge, and etiology of inciting illness.

Results: A total of fifty-six patients were included in the study. Thirty-three patients (59%) were discharged with Stage 2 or worse kidney disease and ten patients (18%) were discharged with Stage 4 or worse kidney disease. Five patients remained dialysis dependent at time of discharge. There was no significant relationship between eGFR at time of discharge and the time interval

between meeting AKI criterion and CRRT initiation using either the CKD-EPI ($p = 0.322$) or MDRD calculation ($p = 0.626$).

Conclusion: In patients receiving ECMO support, timing of CRRT initiation is not associated with degree of renal recovery. This study's methodology was novel in that it utilized AKI diagnosis criterion rather than commencement of ECMO support initiation when measuring timing. Therefore, future research using AKI diagnosis criterion is needed to confirm study results.

Keywords: Acute kidney injury, AKI, Continuous renal replacement, CRRT, Extracorporeal membrane oxygenation, ECMO, renal recovery, eGFR.

Timing of CRRT Initiation Based on AKI Diagnosis in ECMO: A Retrospective Study to Investigate Renal Recovery

Introduction

Problem Description

Patients requiring extracorporeal membrane oxygenation (ECMO) support often experience acute kidney injury (AKI) as a result of their inciting illness and are at high risk for progression to chronic kidney disease (CKD) and renal replacement therapy (RRT) dependence (Forni et al., 2017). In AKI, there is disparity between demand and the ability of the kidneys to meet demand (Ostermann et al., 2016). Renal replacement therapy aims to support that gap until renal recovery can occur. Continuous renal replacement therapy (CRRT) is one of several RRT modalities available that is frequently used in the ICU setting. Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization comprised of multidisciplinary experts that provide practice recommendations for the treatment and prevention of kidney disease based on current research. KDIGO recommends use of CRRT for hemodynamically unstable or brain injured patients in AKI (Class 2B) based on the premise that AKI is amendable to early detection and is potentially reversible (Acute Kidney Injury Work Group [KDIGO], 2012). Patients requiring ECMO support are often hemodynamically unstable and do not tolerate conventional intermittent hemodialysis (IHD). Therefore, CRRT is the preferred method for support in this population (Kuo et al., 2019). However, what is unclear in current research is whether or not timing of CRRT initiation in AKI reduces the incidence of progression to CKD and hemodialysis dependence (KDIGO, 2012).

Available knowledge

A PubMed literature search was conducted using the National Center for Biotechnology database house using the following search terms: “ECMO AND renal replacement AND timing”, “ECMO AND acute kidney injury AND renal replacement”, “renal replacement AND ECMO”, and “CRRT AND ECMO”. Filters applied included research within the past 10 years, adults: 19+ years, and full text available. Three-hundred five abstracts were returned. All abstracts were reviewed and further narrowed based on applicability to study topic. Additional articles reviewed resulted from references contained in the selected PubMed search articles (See Figure 1).

In 2016, two large trials evaluating timing of CRRT initiation and mortality were published which demonstrated conflicting results. The ELAIN trial (Zarbock et al., 2016) reported a significant reduction in 90-day mortality in patients who received early initiation of RRT, whereas the AKIKI trial results demonstrated no difference between early vs late timing (Gaudry et al., 2016). Significant differences between the two studies exist however which may explicate the incongruity in results. First, patients in the ELAIN trial were primarily surgical and overall sicker than primarily medical patients in the AKIKI trial as demonstrated by sequential organ failure (SOFA) score (16 and 10, respectively). Furthermore, the AKIKI trial was a multi-center study as opposed to the single -center design of the ELAIN trial. Single-center studies have frequently been shown to overestimate treatment results. Often, multi-center studies refute treatment benefit previously reported in single-center results (Unverzagt, Prondzinsky, & Peinemann, 2013). Despite differing results, both types of trials are useful. Results from well-designed single center trials test a consistently applied practice strategy thereby limiting variations and subsequent confounders. A multi-center study gives insight to real-world practices and better represents generalized standard of care, albeit perhaps not the best available practices within specific population divisions.

The following year, two meta-analyses which included the AKIKI and ELAIN trials, were published. Bhatt & Das (2017) and Feng et al (2017) analyzed RCTs to assess the impact of early vs late initiation of RRT. Interestingly, both meta-analyses evaluated the same cohort of studies, with the exception of one additional study used in the Bhatt & Das analysis. Primary outcomes in both studies were mortality. Bhatt & Das also included dialysis dependence at 90 days in their primary outcomes. Secondary outcomes were also similar and included ICU and hospital length of stay (LOS). Bhatt & Das further analyzed renal recovery and adverse events between early vs late initiation of RRT. No difference in mortality, ICU LOS, hospital LOS, RRT dependence or adverse events between groups was demonstrated in either meta-analyses, although both cited low to very low quality of evidence using GRADE criteria (Guyatt, Drummond, Meade, Cook, & American Medical Association, 2015). Feng et al (2017) provided further statistical appraisal utilizing trial sequential analysis (TSA). The initial conclusion of their analysis suggested no correlation between early vs late RRT initiation and primary and secondary outcomes. However, TSA failed to demonstrate a Z-curve that crossed both the traditional and sequential monitoring boundaries. Hence, the initial conclusion may be a false-negative finding. Consequently, more trials would need to be included to validate negative findings.

That same year, a systematic review and meta-analysis by Nash et al (2017) evaluated if there was any advantage to one type of RRT modality (CRRT, IHD, or sustained low efficiency dialysis) over another. Results of the analysis revealed no mortality or renal recovery benefit between the different modalities. However, once again the quality of evidence was low in many of the RCTs included due to a lack of appropriate randomization and considerable selection bias. Confounding factors, such as differences in RRT modalities, dosing, initiation times and

definition of AKI also contributed to weakening internal validity for the individual RCTs and subsequent meta-analysis. In addition, a high magnitude of heterogeneity was present revealing a threat to external validity and thus calling into question the generalizability of the analysis results.

Research specific to timing of RRT in the adult ECMO population is scarce and limited primarily to retrospective cohort and case study design. And, much like RRT research in the generalized (non-ECMO) population, results are conflicting. A multicenter retrospective cohort study investigated the risk of mortality associated with timing of CRRT initiation in ECMO patients (Paek et al., 2018). Initially, study results for the entire cohort (n= 296) showed that the late CRRT group had better survival compared to the early group. However, analysis of illness severity between the two groups revealed that the early CRRT group was sicker as indicated by several key indicators (higher creatinine, lower estimated glomerular filtration rate, carbon dioxide, and pH) which also relate to increased risk of mortality (Makris & Spanou, 2016). Propensity score matching was applied to reduce potential confounding biases in the study cohort which substantially reduced the study size of each group (n=47) and thus introduced risk of type 2 error (Streiner & Norman, 2012).

Another retrospective study investigated independent factors that affected mortality in ECMO patients receiving CRRT (He, Zhang, Hu, & Wu, 2018). While timing of CRRT itself was not measured, key clinical indicators and biochemical indices in survivor vs non survivor groups were analyzed. Results demonstrated that fluid balance at ECMO day 3 and day 7 was a positive predictor for mortality. This makes a strong argument for early initiation of CRRT for the purpose of mitigating fluid overload early in the course of ECMO support. Additional research has corroborated the benefits of correcting fluid overload in ECMO including improved

lung function, reduction in ECMO weaning time and overall duration of ECMO support (Azkenazi et al., 2012).

Rationale

As of 2016, the average life expectancy of an adult with CKD who becomes dependent on hemodialysis is only 5-10 years (*Center for Disease Control and Prevention*, 2019). Additionally, annual Medicare expenditures for the treatment of CKD and ESRD was 114 billion dollars (United States Renal Data System, 2018). In lieu of shrinking healthcare resources, chronic kidney disease represents a significant clinical and financial burden. Therefore, strategies to mitigate progression to CKD in the ECMO population must be explored.

Project Aims

Given the high incidence of AKI in those requiring ECMO support, examination of CRRT practices and in particular, when therapy should be initiated, is integral to improving outcomes in this patient population. This project had two specific aims: 1) Investigate to what extent, if any, would timing of CRRT during ECMO support benefit renal recovery? and 2) Explore the application of initiation guidelines for CRRT in ECMO patients.

Methods

This retrospective data review research study received IRB approval from both Legacy Health System and Oregon Health and Science University (IRB # STUDY0002084).

Setting and Context

Legacy Emanuel Medical Center (LEMC) is a 554-bed quaternary care facility in Portland, OR. It is part of a locally owned, private 501(c) non-profit healthcare system consisting of seven hospitals (1600+ licensed beds) ("ECMO Services and Treatments," n.d.). ECMO support was managed by a designated in-house ECMO team consisting of intensivists and a

physician assistant. CRRT was ordered and managed by nephrologists within a single group practice. Patient care and ECMO pump management was provided by a designated ICU team of nurses with a 2:1 ratio.

Interventions

A retrospective chart review was conducted for all ECMO patients ≥ 18 years old admitted to LEMC between January 01, 2016 through December 31, 2019. Chart reviews were conducted electronically via EPIC and Care Everywhere on site at LEMC. Of the identified ECMO patients, those who received CRRT during ECMO support were included in the study. ECMO patients who did not receive CRRT, or who received CRRT after ECMO support was discontinued, were excluded. Patients who did not survive to discharge were excluded as renal recovery could not be appropriately surmised from sCr at time of death. Patients were also excluded if they had pre-existing ESRD.

All data collection was conducted and stored on a secure, password protected computer in accordance with Legacy Health System policy. The author of this doctoral project paper was the primary investigator, performing the chart review and inputting all data measures for subsequent statistical analysis. Quantitative and qualitative data were entered into a Microsoft excel spreadsheet and patient identifiers removed. Statistical analysis was performed by the senior statistician from the Legacy Research team.

Study of the Interventions

Data was intentionally collected from a single site during a four-year period where nursing teams and nephrology providers experienced a high degree of staff consistency with minimal turnover to minimize practice differences that may have confounded results. As such,

results are reflective of an associative relationship and require further research to determine a cause and effect.

Measures

Although several alternative and novel markers for kidney function have been proposed in recent literature (Forni et al., 2017), serum creatinine and eGFR were chosen as indicators of renal function as they are the current measures recommended by KDIGO (2012) guidelines, readily available in most institutions, and commonly performed. Quantitative data collected included patient age, sex, BMI, time from AKI diagnosis to initiation of CRRT, baseline sCr, sCr at time of CRRT initiation and discharge from hospital, and calculation of estimated glomerular filtration rate (eGFR) at hospital discharge. Qualitative data collected included inciting illness requiring ECMO support, documented presence of pre-existing diabetes, hypertension, CKD or cardiovascular disease comorbidities, and criteria met for AKI diagnosis. Data was reviewed by a panel consisting of both renal and ECMO content experts for accuracy and completeness.

Per KDIGO (2012) guidelines, AKI was defined as an increase in serum creatinine (sCr) $\geq$ 0.3 mg/dL in 48 hours, or an increase of 1.5 times the patient's baseline creatinine within seven days, or a urine output $\leq$ 0.5 ml/kg/hr for six hours. Baseline creatinine was defined as the lowest documented serum creatinine within the previous year of admission. If medical records prior to their hospitalization were not available through the outside facility electronic medical record (Care Everywhere), the admission creatinine was used as the baseline value. Estimated glomerular filtration rate (eGFR) was determined by using the sCr at time of hospital discharge and calculated for both the Modification of Diet in renal Disease (MDRD) Study equation (Levey, 2019) and the Chronic Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, 2019).

Analysis

Patient demographics (age, sex, BMI, comorbidities, etiology of inciting illness, criterion for AKI diagnosis, and eGFR at time of discharge) were summarized using descriptive statistics. Linear regression analysis was used to evaluate the relationship between a patient's eGFR at discharge and the time interval between meeting AKI criterion and the start of CRRT. The relationship between the eGFR at discharge and age, sex, BMI, infection type, and the AKI criterion that individuals in the cohort met were evaluated using the one-way analysis of variance (ANOVA) test.

Ethical Considerations

Once chart reviews and data collection were completed, all patients were deidentified including name, medical record number, referring facility, and room number. No patient was contacted for this study. No interventions were performed on patients. All data was stored in accordance with Legacy Health Systems and Oregon Health & Science University data protection policies. No funding was received for this project. As the sole collector of data for this doctoral project, I have no financial disclosure or conflict of interest concerning the material discussed in this final report to disclose.

Results

Patient demographics

A total of 56 patients met study inclusion/exclusion criteria and were included in data analysis. Seventy-three percent (41/56) of patients included in the study were referred and transported from a facility outside of LEMC. The median age of the cohort was 46 years old and median BMI was 34.1. The majority of the cohort patients were Caucasian, two-thirds were male

(n=37), and nearly one-third (n=16) had hypertension as a preexisting comorbidity. The predominant modality of ECMO support was venovenous (VV) (See Table 1).

Primary outcome

Nearly 60% of patients were discharged with Stage 2 or worse kidney disease. Stage 4 (severe) kidney disease, was present in nearly 20% of the patients at discharge (See Figure 2). The median time from AKI diagnosis to CRRT initiation was just under 53 hours (see Figure 3). Using both the CKD-EPI and MDRD eGFR calculation methods, there was no significant relationship between eGFR at discharge and the time interval between meeting AKI criterion and initiation of CRRT ($p = 0.322$, $p = 0.626$ respectively). (See Figure 4 and 5).

Secondary outcomes

The relationship between patient demographics of age, sex, and BMI and eGFR at discharge were analyzed. Again, using both the CKD-EPI and MDRD eGFR calculations, there was no significant relationship between age ($p = 0.085$, $p = 0.246$) (See Figure 6), sex ($p = 0.365$, $p = 0.607$) (See Figure 7) and BMI ($p = 0.273$, $p = 0.092$) (See Figure 8). The decision was made to not analyze the demographic of race due to minimal diversity in the cohort.

The leading criterion met for AKI (per KDIGO guidelines) was a ≥ 0.3 mg/dl increase in sCr within a 48-hour period (See Table 1). Five patients were hemodialysis dependent at time of discharge, although two were making urine and anticipated to continue to progress in their renal recovery and no longer be dialysis dependent in the proceeding weeks. ANOVA analysis demonstrated that there was no significant relationship between eGFR at discharge and AKI criterion met ($p = 0.732$ and $p = 0.677$). (See Figure 9).

Inciting illness was categorized as infectious or noninfectious. The majority of patients required ECMO support due to an infectious etiology. The infectious category was further

delineated as viral, bacterial, viral plus bacterial (mixed), or fungal. Of the patients with an infectious etiology, bacterial was the most common source. All patients in the viral category had either Flu A, Flu B, or both. ANOVA analysis demonstrated a significant relationship between the eGFR at discharge and infection type. Of the different infectious categories, viral infections resulted in lower eGFR at discharge than either bacterial or mixed infections, but only when CPK-EPI calculation was used ($p = 0.039$) (See Figure 10).

Discussion

Summary

While the majority of the cohort did not have kidney disease prior to admission, a significant portion of patients in whom CRRT was utilized, were discharged with renal impairment. This study sought to investigate whether timing of CRRT initiation might confer a benefit in renal recovery in the ECMO population. The study cohort was cared for within an experienced ECMO program. Nephrology and nursing teams delivered effluent dosing at the recommended evidence-based guideline of 20-25 ml/kg/hr (KDIGO, 2012). Unfortunately, results from this research project indicate that timing of CRRT does not appear to ameliorate even partial renal recovery. Accordingly, a recommendation for clinical practice regarding timing of CRRT initiation for the purpose of improving renal recovery from AKI cannot be conferred.

Interpretation

Akin to ECMO, CRRT does not ‘cure’ an illness or injury. Rather, its utility lies in the surrogacy of organ function until the kidneys can recover (Nash, Przech, Wald, & O'Reilly, 2017). As mentioned earlier, several key meta-analyses evaluated CRRT timing in critically ill patients not requiring ECMO support and reported no benefit of early versus late CRRT

initiation, although the quality of evidence was low. For most of the studies used in the analyses, timing was determined by biomarkers such as those used in the criteria for AKI per KDIGO.

In published research regarding timing of CRRT initiation in the ECMO population, the initiation of ECMO was used as "time zero" when measuring the interval for timing (Kuo et al., 2019 and Paek et al., 2018). Because acute kidney injury often occurs early in the progression of illnesses severe enough to warrant ECMO support and typically precedes ECMO cannulation (Azkenazi et al., 2012), the impetus to use clinical criteria for AKI as "time zero" for inquiry was postulated. At the time of this study's origination, no studies using the KDIGO clinical criteria for AKI as "time zero" in patient receiving ECMO were found in the literature search. Comparisons on renal recovery between the two methods of CRRT initiation timing are, therefore, unavailable.

In addition, most of the previous research conducted on use of CRRT in ECMO has used mortality and RRT dependence as outcome measures in evaluating benefit of CRTT (Feng et al., 2017 and Chen et al., 2019). Like the aforementioned research, the results of this study demonstrated only a small portion of patients discharged were RRT dependent. However, the fibrosis from tubule injury in AKI is self-limiting and consequently progression to more severe stages of CKD requires subsequent injury (Venkatachalam, Weinberg, Kriz, & Bidani, 2015). Given the relatively young median age of the cohort, the likelihood of a potential future AKI incident is significant. Therefore, in light of the tremendous implications on life expectancy and healthcare financial burdens that ESRD incurs, lessening milder stages of CKD and mitigating disease progression could be of significant importance as well.

Acute kidney injury requiring RRT has been demonstrated to occur frequently in severe cases of the influenza A and B (Martin-Loeches et al., 2011). Evaluation of inciting illness

etiology and eGFR revealed that the viral category had poorer renal recovery than those of bacterial or mixed infections. This is somewhat surprising as many of the antibiotics used for bacterial infections causing severe illness are nephrotoxic, potentially exacerbating AKI (Fanos & Cataldi, 2013). In this cohort, the viral illness category was comprised exclusively of patients suffering from Influenza A, B or both. These results contradict other research that demonstrated good renal recovery following AKI requiring CRRT in Influenza A patients (Tignanelli et al., 2018). Of note, all patients who remained dependent on RRT at time of discharge were part of the viral category. One plausible explanation for the reduction in renal recovery findings may lie in the deposition of viral antigens in the glomerulus contributing to renal injury. Additionally, an increase in the secretion of Th17 and Th1 cytokines as seen in severe influenza, contributes to adhesion of inflammatory cells to endothelium which in turn incites vasodilatation resulting in worsening renal ischemia (Martin-Loeches et al., 2011).

Limitations

There are several limitations of this study. First, its single center design and lack of ethnic diversity reduces generalizability to other ethnic or geographical populations receiving ECMO support. For instance, it is well established that African Americans with CKD are at higher risk for progression to ESRD than non-Hispanic/whites (Mutner et al., 2012). Subsequently, this study's cohort contained only two African Americans, therefore assessment of CRRT timing and renal recovery cannot be determined in this population due to lack of adequate representation.

Second, as mentioned earlier, the majority of patients were transferred from outside facilities. Treatment considerations for AKI vary in both timing and modalities depending on a facility's culture and resources. It is possible that the time delay in admission to the study site and subsequent treatment decisions from the originating facility may have impacted study

outcomes. Likewise, the single-center design is biased by geographical differences in medical training and practices as well as patient dietary, cultural and lifestyle influences. Again, these differences may present confounders not controlled for in this study.

Finally, given the retrospective design, data utilized for analyses was dependent on documentation in the EMR and any inaccuracies in the documentation of care has the potential to skew study results. When applicable, all available records through Care Everywhere were searched to determine baseline sCr prior to illness onset. This was not achievable in nine of the study cohort patients and therefore the sCR at time admission was substituted for baseline value in statistical analyses. A post-discharge follow-up date would have provided an opportunity to evaluate continued RRT dependence or recovery and theoretically strengthen statistical analysis. However, it was not included in the IRB application and therefore not performed. Of note however, none of the patients who required admission sCr substitution for baseline had a documented history of CKD. Nevertheless, the sCr substitution does alter the time interval between AKI diagnosis and initiation of CRRT, thus potentially influencing study results.

Conclusions

This study sought to investigate associations of timing for the initiation of CRRT for supportive management of AKI in the ECMO population in the hope of identifying strategies to augment renal recovery. Nonmodifiable patient demographics were also investigated to elucidate potential prognostic characteristics for renal recovery following AKI. Acute kidney injury occurs frequently in a myriad of critical illness and subsequent renal recovery is on a continuum, from full recovery of GFR to ESRD and RRT dependence. Partial renal recovery leaves the patient at significant risk for progression to more severe stages of CKD. Patients with little to no recovery face a reduced life expectancy. As a medical community, significant financial burden exists

caring for patients with CKD and ESRD. ECMO is becoming more widely available. Given the high incidence of AKI in these patients, survivors will likely increase the prevalence of CKD progression in the general population.

Acknowledging other findings in investigative research of critical illnesses comprising AKI, such as fluid overload as a positive predictor for mortality, the role of early CRRT merits further inquiry. Although this novel study did not find an association between timing of CRRT initiation and renal recovery, knowledge gained by studying the question remains valuable and underpins the need for further research using analogous methods and diagnostic criteria to confirm its findings.

Acknowledgements

I would like to extend a very gracious thank you to several people whose help was invaluable in the completion of this research. First, to my preceptor and mentor, Rob Brookshire, PA-C. Thank you for selflessly sharing your knowledge, advocacy, time and wisdom. You represent the very best that advanced practice providers have to offer, and I am forever grateful to have had the opportunity to learn from you! To Ashley Blatchley, my nursing director. Your leadership transcended a culture naïve to the role of advanced practice providers, helping break down barriers and open doors for the advancement of our profession. To Shaban Demirel, Legacy Health statistician. Your assistance helped make sense of it all and you were such a joy to work with and learn from. To my academic director Dr. Benjamin Schultze, your pragmatic approach helped keep me “out of the weeds”. And finally, to my husband. Your patience, sacrifice and support helped turn an aspiration into a reality.

References

Center for Disease Control and Prevention: Chronic kidney disease in the United States, 2019. (2019). Retrieved from https://www.cdc.gov/kidneydisease/publications-resources/2019-national-facts.html

2018 USRDS annual data report: Epidemiology of kidney disease in the United States. (2018). Retrieved from https://www.usrds.org/2018/view/Default.aspx

Acute Kidney Injury Work Group. (2012). KDIGO clinical practice guideline for acute kidney injury. Retrieved from https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf

Azkenazi, D., Selewski, D., Paden, M., Cooper, D., Bridges, B., Zapitelli, M., & Fleming, G. (2012). Renal replacement therapy in critically ill patients receiving extracorporeal membrane oxygenation. *Clinical Journal of the American Society of Nephrology*, *7(8)*, 1328-1336. Retrieved from https://cjasn-asnjournals-org.liboff.ohsu.edu/content/7/8/1328

Bhatt, G., & Das, R. (2017). Early versus late initiation of renal replacement therapy in patients with acute kidney injury: A systematic review & meta-analysis of randomized controlled trials. *BMC Nephrology*, *18(78)*, 1-14. http://dx.doi.org/10.1186/s12882-017-0486-9

Chen, S., Lu, Y., Lee, C., Chou, A., Wu, V., Chang, S., ... Chang, C. (2019). Long-term outcomes after extracorporeal membrane oxygenation in patients with dialysis requiring acute kidney injury: A cohort study. *PLoS ONE*, *14(3)*. http://dx.doi.org/10.1371/journal.pone.0212352

ECMO services and treatments. (n.d.). Retrieved September 20, 2019, from https://www.legacyhealth.org/for-health-professionals/refer-a-patient/ECMO-for-providers/services-and-treatments.aspx

Fanos, V., & Cataldi, L. (2013). Renal transport of antibiotics and nephrotoxicity: a review. *Journal of Chemotherapy*, *13 (5)*, 461-472. http://dx.doi.org/10.1179/joc.2001.13.5.461

Feng, Y., Yang, Y., Han, X., Zhang, F., Wan, D., & Guo, R. (2017). The effect of early vs late initiation of renal replacement therapy in patients with acute kidney injury: A meta-analysis with trial sequential analysis of randomized controlled trials. *PLoS ONE*, *12(3)*. http://dx.doi.org/10.1371/journal.pone.0174158

Forni, L., Darmon, M., Ostermann, M., Straaten, H., Petilla, V., Prowle, J., ... Johannidis, M. (2017). Renal recovery after acute kidney injury. *Intensive Care Medicine*, *43(6)*, 855-866. http://dx.doi.org/10.1007/s00134-017-4809-x

Gaudry, S., Hajage, D., Schortgen, F., Martin-Lefevre, L., Pons, B., Boulet, E., ... Dreyfuss, D. (2016). Initiation strategies for renal replacement therapy in the intensive care unit. *The New England Journal of Medicine*, *375(19)*, 1899-1902. http://dx.doi.org/10.1056/NEJMc1610500

Guyatt, G., Drummond, R., Meade, M., Cook, D., & American Medical Association (2015). *User's guide to the medical literature: A manual for evidence-based clinical practice* (3rd ed.). New York, NY: McGraw-Hill Education.

He, P., Zhang, S., Hu, B., & Wu, W. (2018). Retrospective study on the effects of the prognosis of patients treated with extracorporeal membrane oxygenation combined with continuous renal replacement therapy. *Annals of Translational Medicine*, *6(23)*, 455. http://dx.doi.org/10.21037/atm.2018.11.12

Kuo, G., Chen, S., Fan, P., Wu, V., Chou, A., Lee, C., ... Chang, C. (2019). Analysis of survival after initiation of continuous renal replacement therapy in patients with extracorporeal membrane oxygenation. *BMC Nephrology*, *20*, 1-9. http://dx.doi.org/10.1186/s12882-019-1516-6

Levey, A. (2019). CKD-EPI Equations for GFR (2.2.7) [Mobile application software]. Retrieved from www.MDCalc.com

Levey, A. (2019). MDRD GFR Equation (2.2.7) [Mobile application software]. Retrieved from www.MDCalc.com

Makris, K., & Spanou, L. (2016). Acute kidney injury: Definition, pathophysiology and clinical phenotypes. *The Clinical Biochemist Reviews*, *37(2)*, 85-98. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5198510/

Martin-Loeches, I., Papiol, E., Rodriguez, A., Diaz, E., Zaragoza, R., Granada, R., & Rello, J. (2011). Acute injury in critical ill patients affected by influenza A (H1N1) virus infection. *Critical Care*, *15(1)*, 1-10. http://dx.doi.org/10.1186/cc10046

Matsushita, K., Mahmoodi, B., Woodward, M., Emberson, J., Jafar, T., Ha Jee, S., & Levey, A. (2012). Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *The Journal of the American Medical Association*, *307 (18)*, 1941-1951. http://dx.doi.org/10.1001/jama.2012.3954

Mutner, P., Newsome, B., Kramer, H., Peralta, C., Yongin Kim, D., Keife, C., & Lewis, C. (2012). Racial differences in the incidence of chronic kidney disease. *Clinical Journal of American Society of Nephrology*, *7*, 101-107. http://dx.doi.org/10.2215/CJN.06450611

Nash, D., Przech, S., Wald, R., & O'Reilly, D. (2017). Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. *Journal of Critical Care*, *41*(), 138-144. http://dx.doi.org/10.1016/j.jcrc.2017.05.002

Ostermann, M., Johannidis, M., Pani, A., Floris, M., De Rosa, S., Kellum, S., & Ronco, C. (2016). Patient selection and timing of continuous renal replacement therapy. *Blood Purification*, *42(3)*, 224-247. http://dx.doi.org/10.1158/000448506

Paek, J., Park, S., Lee, A., Park, S., Chin, H., Na, K., ... Kim, S. (2018). Timing of initiation of sequential continuous renal replacement therapy in patients on extracorporeal membrane oxygenation. *Kidney Research and Clinical Practice*, *37*, 239-247. http://dx.doi.org/10.23876/j.krcp.2018.37.3.239

Streiner, D., & Norman, G. (2012). The pros and cons of propensity scores. *CHEST*, *142(6)*, 1380-1382. http://dx.doi.org/10.1378/chest.12-1920

Tignanelli, C., Wiktor, A., Vatsaas, C., Sachdev, G., Heung, M., Park, P., & Napoitano, L. (2018). Outcomes of acute kidney injury in patients with severe ARDS due to influenza A(H1N1) PDM09 virus. *American Journal of Critical Care*, *27 (1)*, 67-73. http://dx.doi.org/10.4037/ajcc2018901

Unverzagt, S., Prondzinsky, R., & Peinemann, F. (2013). Single-center trials tend to provide larger treatment effects than multicenter trials: A systematic review. *Journal of Clinical Epidemiology*, *66*, 1271-1280. http://dx.doi.org/10.1016/.jclinepi.2013.05.016

Venkatachalam, M., Weinberg, J., Kriz, W., & Bidani, A. (2015). Failed tubule recovery, AKI-CKD transition, and kidney disease progression. *Journal of the American Society of Nephrology*, *26 (8)*, 1765-1776. http://dx.doi.org/10.1681/ASN.2015010006

Zarbock, A., Kellum, J., Schmidt, C., Van Aken, H., Wempe, C., Pavenstadt, H., ... Meersch, M. (2016). Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury. *Journal of American Medical Association*, *315(20)*, 2190-2199. http://dx.doi.org/10.1001/jama.2016.5828

APPENDIX A

Figure 1.

Literature review

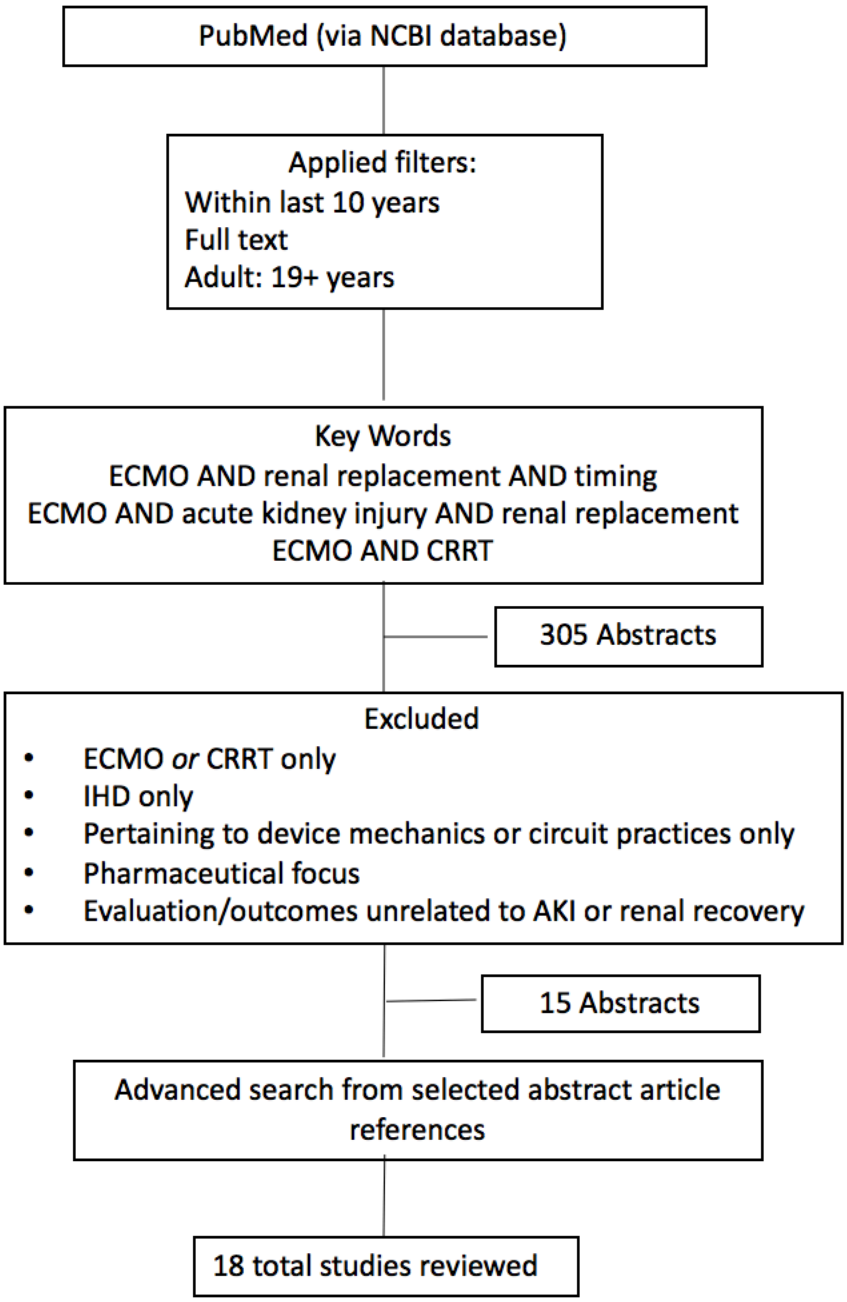


Table 1

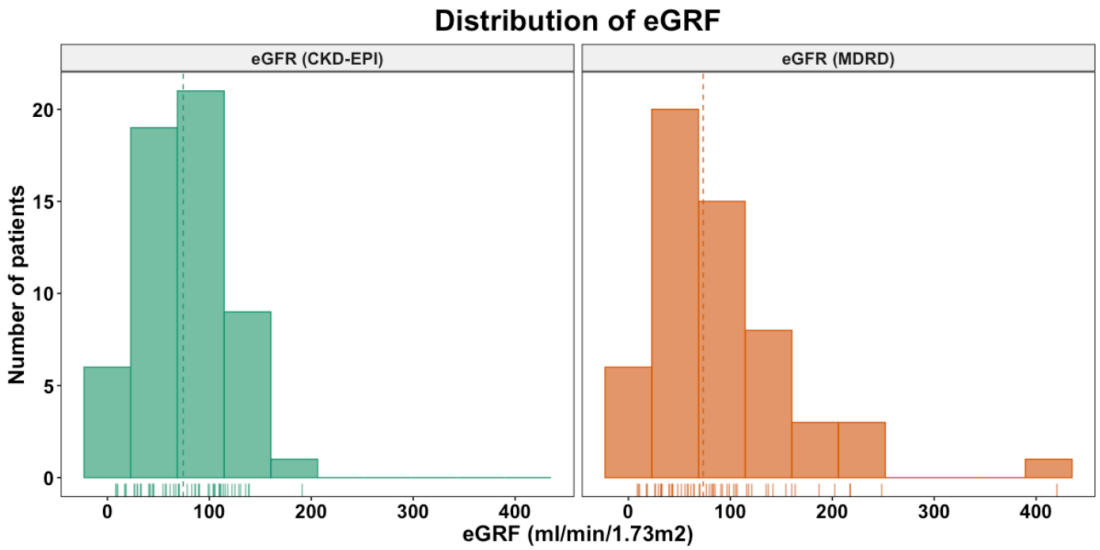
Patient Demographics

Characteristic	*n*=	(%)	Value
Age yrs old			
Median ± SD			46 ± 13
Interquartile Range			19-69
Sex			
Male	19	(34)	
Female	37	(66)	
BMI			
Median ± SD			34.1 ± 9.8
Interquartile range			19-62.4
Race			
nonHispanic/White	46	(82.1)	
African American	2	(3.6)	
Pacific Islander	2	(3.6)	
Native American	2	(3.6)	
Hispanic	1	(1.7)	
Asian	1	(1.7)	
Not disclosed	2	(3.6)	
Comorbidity			
Cardiovascular disease	7	(12.5)	
Chronic kidney disease *(not including ESRD)*	4	(7)	
Diabetes	9	(16)	
Hypertension	16	(28.5)	
Mode of ECMO Support			
VenoVenous (VV)	49	(87.5)	
VenoArterial (VA)	7	(12.5)	
Etiology of Inciting Illness			
Infectious	40	(71.4)	
Viral	10	(17.8)	
Bacterial	20	(35.7)	
Bacterial + Viral	9	(16)	
Fungal	1	(1.7)	
Noninfectious	11	(19.6)	
Undetermined	5	(8.9)	
AKI Criterion Met			
sCr increased by ≥ 0.3 mg/dL in 48 hours	38	(69.1)	
sCr increased by 1.5x baseline within 7 days	6	(10.9)	
Urine output < 0.5 ml/kg/hr x 6 hrs	11	(20)	
Serum Creatinine (sCr)			
Baseline sCr ± SD			0.9 ± 0.93*
sCr ± SD at time of CRRT initiation			2.39 ± 1.64
Discharge sCr ± SD			1.04 ± 1.43
eGFR at discharge ± SD			
MDRD			73.35 ± 73.22
CKD-EPI			74.35 ± 41.84
Hemodialysis Dependence at Discharge	5	(9)	

SD = standard deviation, BMI = body mass index, ECMO = extracorporeal membrane oxygenation, AKI = acute kidney injury, sCr = serum creatinine, eGFR = estimated glomerular filtration rate, MDRD = Modification of Diet in Renal Disease Study equation, CKD-EPI = Chronic Kidney Disease Epidemiology collaboration equation, *admitting sCr used in 9 patients due to unavailability of prehospitalization records.

Figure 2

Distribution of eGFR



---

eGFR (CKD-EPI):

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
8.10	41.00	74.35	75.77	109.65	191.10

eGFR (MDRD)

Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
8.70	39.88	73.35	89.81	116.58	420.40

Figure 3

Distribution of interval hours

```
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  6.267  20.117  52.767  76.252  81.892 340.800
```

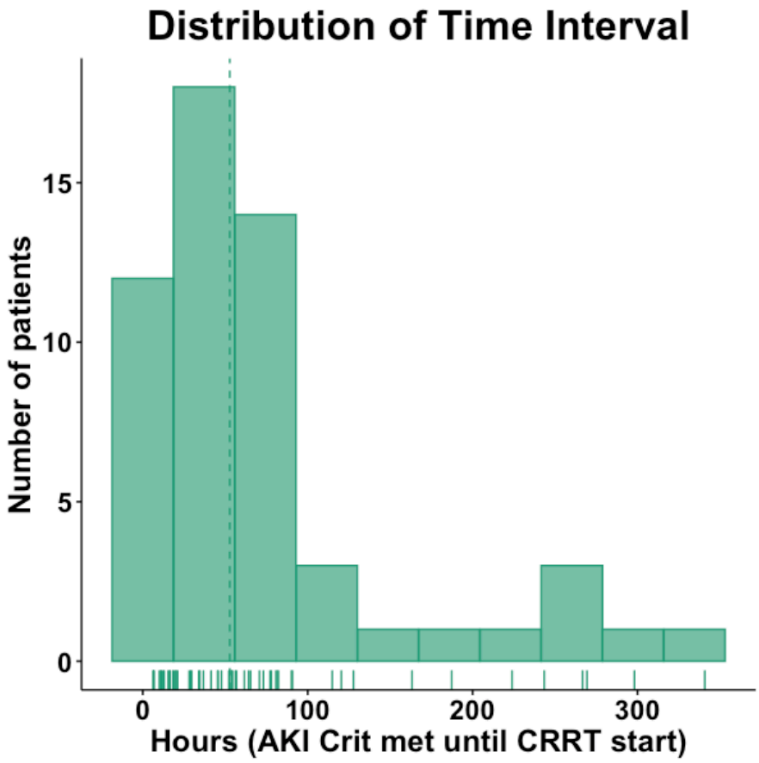


Figure 4

eGFR at discharge (CPK-EPI)

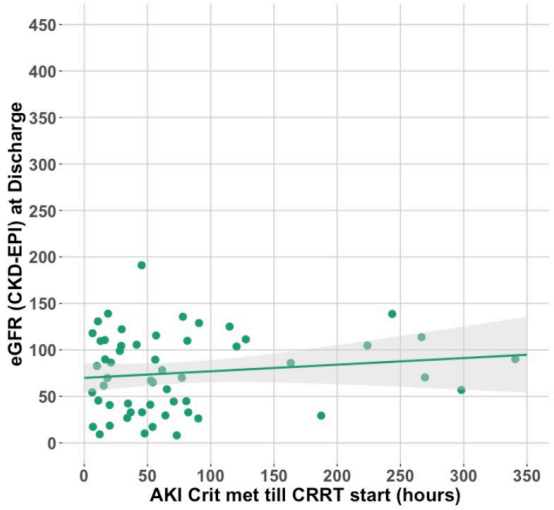


Figure 5

eGFR at discharge (MDRD)

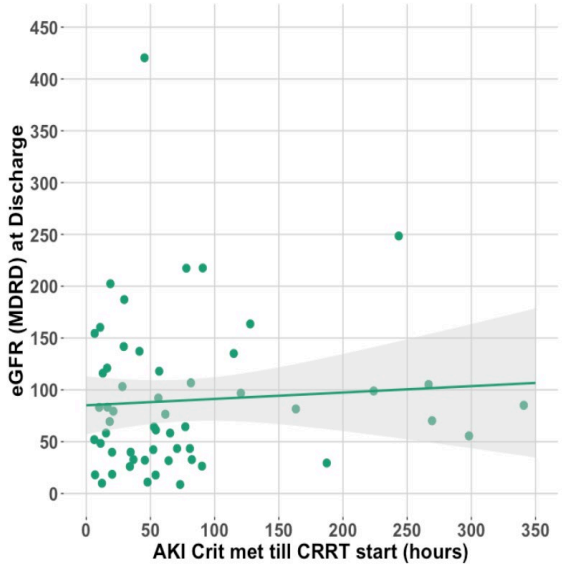
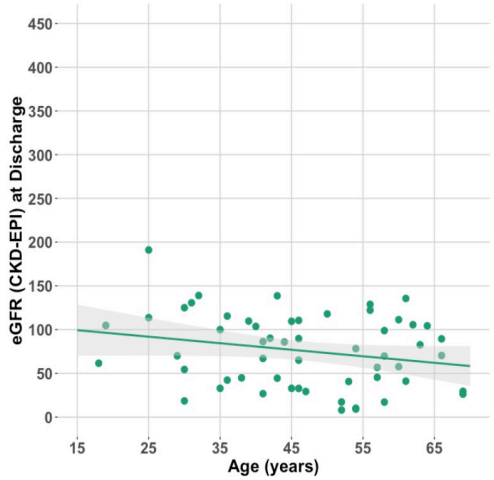


Figure 6

Age and eGFR (CKD-EPI)



Age and eGFR (MDRD)

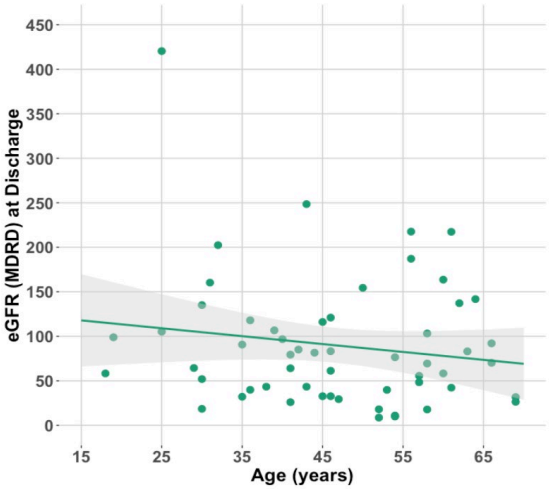
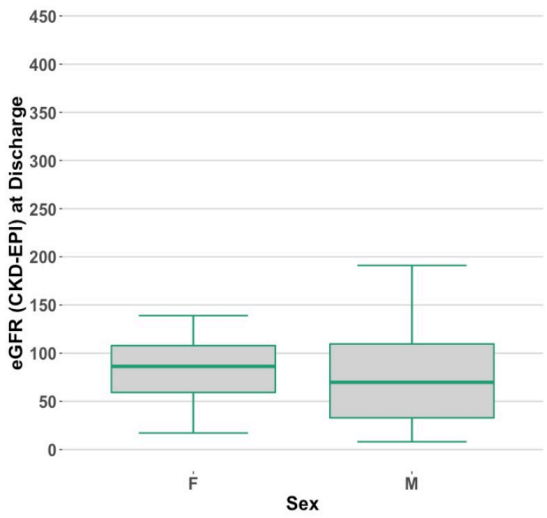


Figure 7

Sex and eGFR (CKD-EPI)



Sex and eGFR (MDRD)

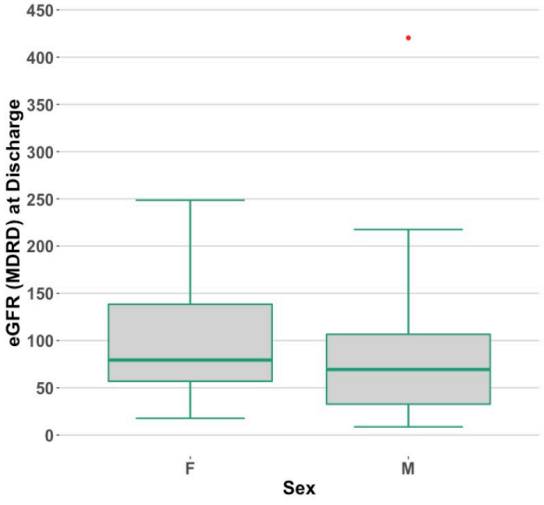


Figure 8

BMI and eGFR (CKD-EPI) *BMI and eGFR (MDR*

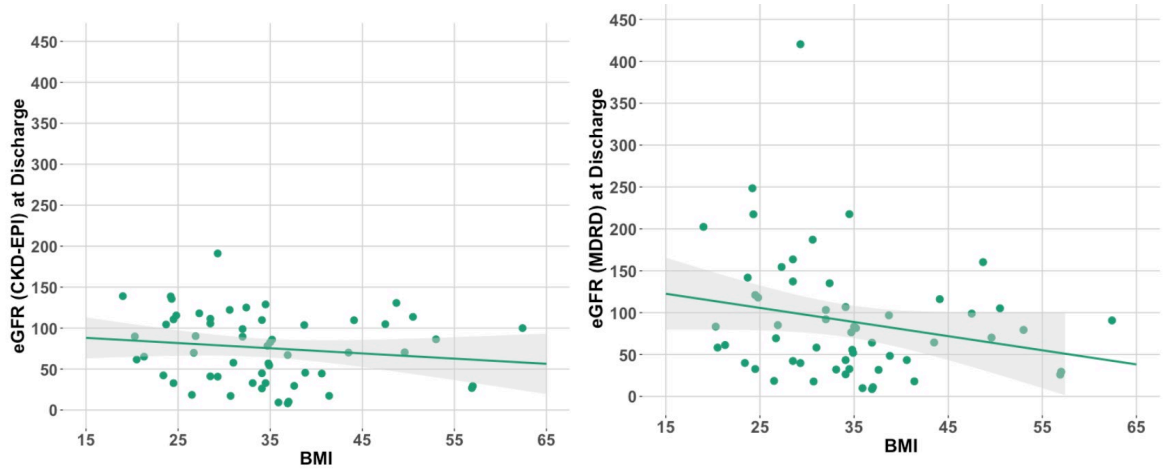
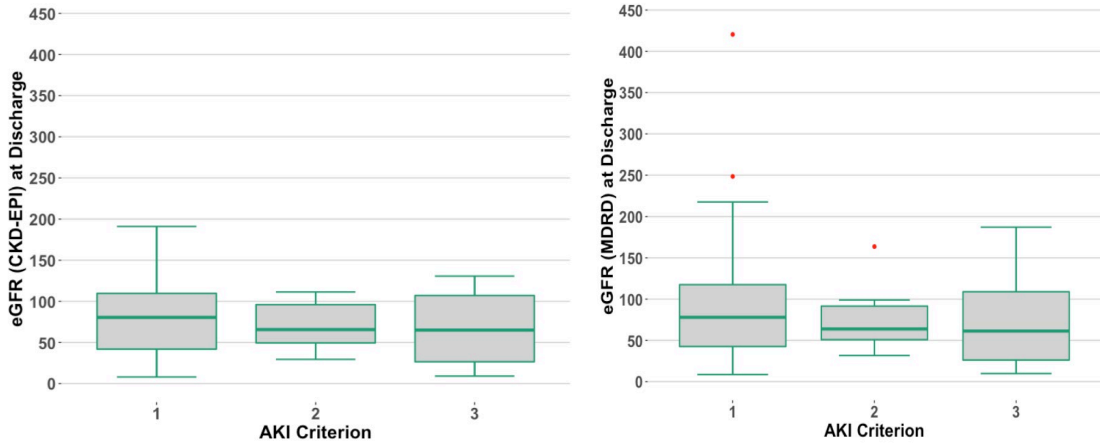


Figure 9

AKI criterion (CKD-EPI) *AKI criterion (MDRD)*



Criterion 1= sCr increased by ≥ 0.3 mg/dL in 48 hours

Criterion 2 = sCr increased by 1.5x baseline within 7 days

Criterion 3 = Urine output < 0.5 ml/kg/hr x 6 hrs

Figure 10

Type of infection and eGFR (CKD-EPI) *Type of infection and eGFR (MDRD)*

Infectious N=40 (total) n= Noninfectious n=11 Undetermined n=5

Viral 10

Bacterial 20