Prognostication in Very Old Intensive Care Patients with Acute Kidney Injury

Marc Romain MBBCh[1], Michael Beil MD[1], Josh Mormol[1], Ilana Stav[1], Tali Liberman[1], Peter Vernon van Heerden MD[2], and Sigal Sviri MD[1]

[1]Department of Medical Intensive Care, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, Israel
[2]Department of Anesthesiology, Hadassah Medical Organization and Faculty of Medicine, Hebrew University of Jerusalem, Israel

ABSTRACT **Background:** Acute kidney injury (AKI) is a risk factor for morbidity and mortality during critical illness especially in very old patients admitted to intensive care units.

Objectives: To identify prognostic markers for AKI patients.

Methods: This single-center retrospective study was based on a patient registry of a medical intensive care unit. Hospital records of patients aged 80 years or older admitted between 2005 and 2015 were examined. Patients who developed AKI according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines within 4 days of admission were included in this study.

Results: The study comprised 96 patients with AKI and 81 age- and sex-matched controls without AKI. Mean acute physiology and chronic health evaluation (APACHE) II score was 30 with an ICU mortality of 27% in very old patients with AKI. The odds ratio of hospital mortality for these patients was 5.02 compared to controls (49% vs. 16%). APACHE II score and fluid balance in the first 2 days of ICU admission were the strongest predictors of ICU mortality with an area under the receiver operating characteristic of 0.76. Of the 47 patients with AKI who survived hospital admission, 30 were discharged home.

Conclusions: Mortality was increased in very old ICU patients with AKI. Among survivors, two-thirds returned home.

IMAJ 2023; 25: 272–277

KEY WORDS: acute kidney injury (AKI), fluid overload, intensive care unit (ICU), very old

Acute kidney injury (AKI) is a risk factor for morbidity and mortality during critical illness [1]. Age-related changes in renal anatomy and physiology expose very old intensive care patients (VOP, age ≥ 80 years) to an increased risk for AKI [2]. Moreover, multi-morbidity and polypharmacy, which are prevalent in this age group, may further increase that risk. Limited information exists about the short-and long-term mortality in these patients after AKI. Prognostication is based on studies that involved younger patients [3] and, hence, may be imprecise when applied to the very old patients.

Intensive care can provide a survival benefit to some VOP [4]. However, this group of patients is very heterogeneous regarding resilience and response to intensive care treatment. Importantly, elderly survivors of AKI often have a reduced functional capacity and quality of life after discharge from hospital. They consume substantially greater healthcare resources than the general population as a result of longer hospitalizations and rehospitalizations [5]. Thus, a robust decision-making process is especially important in VOP to prevent inappropriate interventions [6] or underutilization of appropriate technologies. Chronological age is considered a poor predictor of outcome [7]. Additional predictors that would ideally be available early in the course of a critical illness are required to inform decision-making. We investigated prognosticators in VOP who developed AKI within 4 days of admission to a medical intensive care unit.

PATIENTS AND METHODS

A retrospective review of the medical intensive care unit (MICU) database and charts as well as the electronic health records system of the Hadassah Medical Center was performed on records of patients 80 years and older (VOP) who had been admitted to the MICU between 1 January 2005 and 31 December 2015. Length of survival was determined from hospital files or from Ministry of Interior records. Permission was obtained from the institutional review board (Approval number 0157-17-HMO). We screened for patients 80 years of age or older who were transferred to the MICU within 72 hours of hospital admission and had a serum creatinine level of 140 μmol/l or higher. This value represents a 1.5-fold increase in the upper limit of the normal range for creatinine in the hospital and is the upper limit for initial scoring using the acute physiology and chronic health evaluation (APACHE) II score. The range for hospital admission creatinine values for this group was 42 to 798 μmol/l. These patients were then rechecked to confirm that they fulfilled the criteria for AKI according to the Kidney Disease: Improving Global Outcomes (*KDIGO*) guidelines [8] within the first 4 days after ICU admission. As per the

KDIGO guidelines, the patients were divided into 3 groups: AKI stage 1, 2, and 3, based on both creatinine and urine output criteria. Urine output criteria was based on an estimated 80 kg body weight (< 40 ml/hr = urine output of 0.5 ml/kg/hr) for all patients. Patients who were on chronic dialysis or who were discharged from the ICU within 24 hours or required renal replacement therapy (RRT) within 24 hours of ICU admission were excluded [Figure 1]. These patients were excluded as 24 hours is insufficient time to investigate the effect of parameters on predictive modelling, such as fluid balance. The control group consisted of age and gender matched VOP who were not in AKI or who were not receiving chronic dialysis.

Statistical analysis was performed using JMP_Pro version 14 (SAS Institute Inc., Cary, NC, USA). The distribution of continuous variables is presented as means and standard deviation (SD) for normally distributed data and as medians and ranges for all other data. Comparison of normally distributed continuous variables between groups was performed using Student's *t*-test. The Wilcoxon signed rank test was used for comparing other continuous variables. Comparison of categorical values was performed using the chi-square test. A *P*-value of < 0.05 was considered statistically significant. Kaplan–Meier analysis was performed comparing long-term survival between groups. Cox regression analysis was used to evaluate parameters influencing survival in the AKI group. The area under the receiver operating characteristic curve (AUROC) for the Cox regression analysis was calculated including the 95% confidence interval (95%CI).

RESULTS

During the period 2005 to 2015, 546 (14.2%) of the 3965 patients admitted to the MICU were 80 years or older (VOP). Of these, 96 (17.6%) fulfilled the inclusion criteria for this study [Figure 1]. Of note, 23 patients with AKI who were admitted to the ICU for less than 24 hours, and were therefore excluded from the study group, 18 (78%) died during their ICU admission. In addition, of the 13 patients who were dialyzed during the first 24 hours of admission, 6 (46%) died the in ICU and the remaining 7 were weaned from dialysis in the ICU and survived until hospital discharge.

A further 81 VOP without AKI were included in a control group. The demographic data as well as admission diagnoses and chronic co-morbidities for both groups are shown in Table 1. Other than renal conditions, infections were significantly less prevalent in the control group. The overall severity of the critical condition as documented by the APACHE II score was significantly lower in the control group. When the APACHE II score was calculated without the renal component for both groups, the APACHE II score was still significantly lower in the control group [Table 1].

Mortality was significantly increased, and median time of survival was significantly decreased in patients with AKI in comparison to controls [Table 1]. The odds ratio for hospital mortality in the presence of AKI was 5.02 (95%CI 2.45–10.26) compared to patients without AKI.

To match for severity of illness, a sub-group of the control

Figure 1. Flow chart indicating the inclusion and exclusion criteria

AKI = acute kidney injury, ICU = intensive care unit, KDIGO = Kidney Disease: Improving Global Outcomes, LOS = length of stay, MICU = medical intensive care unit

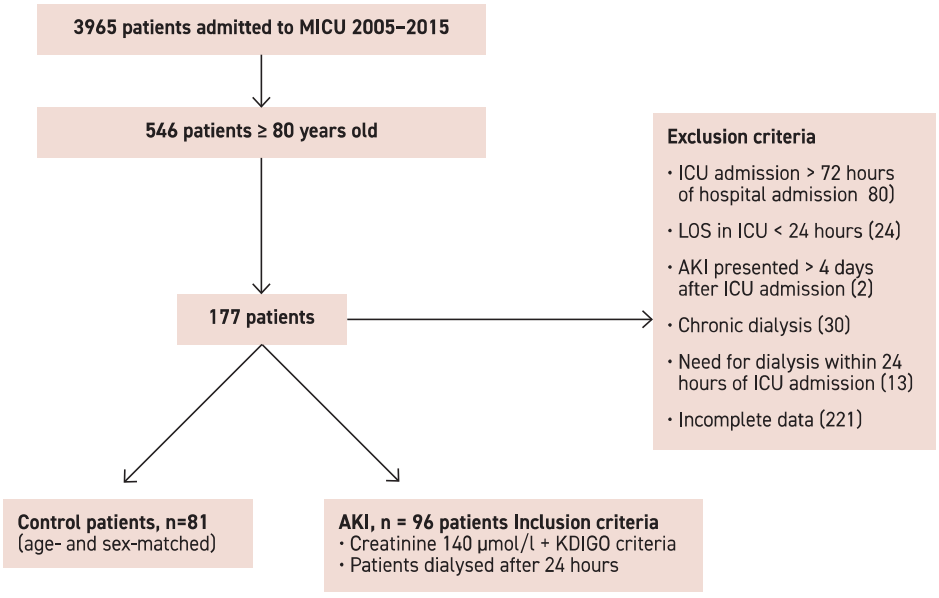

Table 1. Patient characteristics and outcome

	Patients with AKI (n=96)	Controls (n=81)	*P*-value
Age in years, mean ± SD	85.2 ± 3.7)	85.5 ± 3.9	0.68
Male sex	54 (56.3%)	37 (45.7%)	0.16
APACHE II score, mean ± SD	30.1 ± 7.0	21.1 ± 7.1	**< 0.0001**
APACHE II score (without renal component), mean ± SD	27.9 ± 7.06	21.1 ± 7.1	**< 0.0001**
Admission diagnoses			
Pneumonia	28 (29.2%)	27 (33.3%)	0.5
Non-infectious respiratory	11 (11.5%)	26 (32.1%)	**0.0013**
Gastrointestinal, hepatic	14 (14.6%)	12 (14.8%)	0.4
Cardiac	24 (25 %)	14 (17.3%)	0.26
Renal	38 (39.6%)	0	**< 0.0001**
Infections	46 (47.9%)	11 (13.6%)	**< 0.0001**
Metabolic / Other	18 (18.7%)	19 (20.9%)	0.7
Chronic conditions			
Chronic respiratory failure	21 (21.9%)	20 (24.7%)	0.65
Cardiovascular disease	64 (66.7%)	45 (55.6%)	0.13
Chronic kidney disease	36 (37.5%)	6 (7.4%)	**< 0.0001**
Neurological	13 (13.5%)	16 (19.7%)	0.26
Hemato/oncology	15 (15.6%)	14 (17.3%)	0.76
Other	15 (15.6%)	16 (19.7%)	0.6
Length of stay (days), median / mean ± SD			
ICU	5.6 / 8.8 ± 8.6	3.96 / 7.3 ± 8.05	0.21
Hospital	15.5 / 19.1 ± 15.6	11.7 / 16.9 ± 15.3	0.34
Outcome			
Died in ICU	27 (28.1%)	7 (8.64%)	**0.001**
Died in hospital	47 (48.9%)	13 (16.1%)	**< 0.0001**
Median / mean ± SD, time of survival, days	57 / 413 ± 694.6	783 / 899 ± 926	**0.0002**

ICU = intensive care unit, SD = standard deviation
Bold indicates significance

patients with a mean APACHE II of 30 (n=24) was extracted and ICU and hospital outcomes in these patients were compared with outcomes in the AKI group. Although there was a tendency for increased ICU and hospital mortality in the AKI group (28% vs. 25% for ICU mortality, respectively; 49% vs. 38% for hospital mortality, respectively) this did not reach statistical significance.

Twenty of the patients with AKI (20.8%) required RRT during their ICU stay. Fourteen of these patients started dialysis within the first 2 days of ICU admission. Eleven (72%) of the patients on RRT died in the hospital, 8 in the ICU.

Within the group of patients with AKI, there was no significant difference in age or prevalence of chronic kidney disease (CKD) between survivors and non-survivors. The KDIGO stage and peak levels of serum creatinine were not statistically different between these two groups [Table 2]. Patients who were exposed to nephrotoxins, including aminoglycosides, contrast media, and non-steroidal anti-inflammatory drugs had a significantly lower hospital survival (12 vs. 37, $P = 0.001$). Moreover, the fluid balance differed significantly between survivors and non-survivors after both 2 and 4 days. On day 2, non-survivors had a fluid balance of more than 2 liters greater than the survivors did. On day 4, the difference was even greater with non-survivors having over a 3-liter positive fluid balance [Table 2].

Table 3 shows the discrimination of various models for survival prediction by their AUROC in the AKI group. The most inclusive model includes fluid balance and APACHE II.

Of the 47 patients with AKI who survived hospital admis-

Table 2. Patients with AKI: characteristics of survivors vs. non-survivors

	ICU outcome		Hospital outcome	
Parameter	**Survived**	**Died**	**Survived**	**Died**
KDIGO stage (number of patients)				
1	16	4	13	7
2	30	8	22	16
3	22	15	13	24
P-value (survivors vs. non-survivors)		0.1		**0.049**
Peak levels of serum creatinine (μmol/l) during the first 4 days in ICU, mean ± SD	291 ± 144	298 ± 133	296.5 ± 158	289.8 ± 122
P-value		0.8255		0.8163
Exposure to nephrotoxins				
Yes	23 (33.3%)	16 (59.3%)	12 (24.5%)	27 (57.5%)
No	46 (66.7%)	11 (40.7%)	37 (75.5%)	20 (42.5%)
P-value		**0.02**		**0.001**
Administration of vasopressors				
Yes	46 (66.7%)	21 (77.8%)	32 (65.3%)	35 (74.5%)
No	23 (33.3%)	6 (22.2%)	17(34.7%)	12 (25.5%)
P-value		0.28		0.33
Mean arterial pressure in mmHg, mean ± SD	55.7 ± 10.6	49.9 ± 12.6	55.9 ± 9.9	52.1 ± 12.6
P-value		**0.0425**		0.0983
Urine output, mean ± SD				
During days 1 and 2	2115 ± 1666	1025 ± 947	2380 ± 1790	1212 ± 1028
P-value		**0.0001**		**0.0002**
During days 3 and 4	2970 ± 1867	1437 ± 1315	3168 ± 1994	1957 ± 1476
P-value		**0.0001**		**0.0016**
Fluid balance in ml, mean ± SD				
After day 2	2278 ± 2593	4661 ± 3552	2072 ± 2709	3862 ± 3184
P-value		**0.003**		**0.0039**
After day 4	849 ± 2483	3931 ± 3560	362 ± 2231	2986 ± 3289
P-value		**0.001**		**< 0.0001**

ICU = intensives care unity, KDIGO = Kidney Disease: Improving Global Outcomes, SD = standard deviation
Bold indicates significance

Table 3. Area under the curve obtained by logistic regression models for intensive care unit and hospital mortality in the acute kidney injury group (survivors vs. non-survivors)

Model	ICU mortality	Hospital mortality
APACHE II	0.71	0.69
FB D1D2 + APACHE II	0.7 0.76	0.67 0.74

The left column depicts the clinical characteristics included in the model
APACHE II = acute physiology and chronic health evaluation II, FB D1D2 = fluid balance day 1 and day 2, ICU = intensive care unit

sion, 30 (63%) were discharged home, two (4%) were discharged to a long-term ventilation facility, and 15 (32%) were discharged to various levels of nursing care facilities. Only one patient continued dialysis post-discharge, and two patients in the AKI group started dialysis within 6 months of discharge.

DISCUSSION

AKI is an established predictor of morbidity and mortality in ICU patients [9]. The prevalence of AKI in adults is difficult to estimate due to differences in the implementation of diagnostic

criteria but may be as high as 66% [9]. It constitutes a substantial challenge in very elderly patients since advanced age is a risk factor for both developing AKI as well as for morbidity and mortality after AKI [9,10]. AKI in these patients involves a variety of pathophysiological processes [9] proceeding on the background of aged kidneys, which are characterized by an altered tolerance to hypoxia and inflammatory insults [11]. Moreover, interactions with other acute conditions are most pronounced in the context of multi-morbidity, which is found in 90% of VOP [12] and may have an additional impact on long-term outcome [13]. Despite the importance of these topics, there are few studies that investigated the sequelae of AKI in the very elderly [10,14-16]. One cohort of patients with AKI who underwent hip fracture surgery demonstrated higher short- and long-term mortality, delayed surgery, and longer hospitalizations. The mean age in the cohort was 72.6 years [16].

In this retrospective study on VOP with AKI, we found significantly reduced short- and long-term survival compared to age- and gender-matched controls without AKI. Both groups of patients showed a similar distribution of chronic co-morbidities, except for CKD. Of note, there is a large variation of reported data between AKI studies despite standardized criteria (KDIGO guidelines [8]) to diagnose this condition [9]. The variability of the case mix within the investigated patient populations is a major source for that heterogeneity and underlines the importance of appropriate control groups for the assessment of risk factors and outcome measures.

The odds ratio was 5 for hospital mortality in VOP due to AKI. This result is higher than previously reported in a large study on hospitalized elderly patients [17]. However, the patients in the report by Ishani et al. [17] were younger and managed outside ICUs. To some extent, the increase of mortality due to AKI could reflect the increased severity of the critical condition with AKI being an early visible marker. This hypothesis is supported by the finding that the quantitative difference between the mean APACHE II score of AKI patients and that of controls exceeds the maximum difference that could be caused by the renal component (serum creatinine level) of this score alone. As we have shown, corrected APACHE II scores without the renal aspect in the AKI group were still significantly higher than the controls. Alternatively, AKI might be the leading condition in some patients causing impairment of other organs, that is by promoting a systemic inflammatory response [9]. However, such a causality is difficult to prove in multi-morbid patients.

Improving prognostication would facilitate decision-making about further management of patients in the ICU. Thus, we identified characteristics in VOP with AKI that may predict non-survival at an early stage. These characteristics include pre-existing features of patients, such as demographics or chronic conditions and clinical features of the acute condition. As expected, exposure to nephrotoxins or hypotensive episodes were found to be more prevalent in non-survivors. Importantly, the KDIGO stage of AKI or the peak creatinine level alone did not differ significantly between survivors and non-survivors of AKI in our study. However, previous investigations in younger patient populations in the ICU (18) or in non-ICU settings [14,15] reported a significant association between these two parameters and survival. The negative findings in our study suggest that other conditions override the contribution of AKI on outcome in this age group and setting. CKD, for example, is known to attenuate the mortality difference between AKI stages [9].

A substantially negative or positive fluid balance in intensive care patients seems to be correlated with a lack of recovery from AKI that was associated with increased mortality [19-21]. Zhang et al. [19] showed that an increase by only 1 liter over 72 hours was associated with an increase in mortality. A study by Margolis and colleagues [21] using a cohort of patients with ST-elevation myocardial infarction (STEMI) showed that for every 1-liter increase in positive fluid balance, the adjusted possibility for recovery of renal function decreased by 21% [21]. In our study, the fluid balance during days 1–2 and 3–4 was significantly higher in non-survivors compared to survivors. Non-survivors had a greater than 2-liter positive fluid balance when compared to survivors. The positive fluid balance was due to increased fluids received and due to decreased fluid output. Importantly, the fluid balance during day 1 and 2 was found to have a similar value in predictive modelling as the APACHE II score. This further emphasizes the impact of AKI on mortality in VOP.

This study is important as it focuses on the very elderly in the ICU. Despite overall Apache II score being high and the presence of AKI, 49% of these patients survived and many (63%) were discharged home in a good functional state. This finding was also reported by Druml and colleagues [22] that despite increased disease severity over the years, age is not an important determinant of survival in patients with AKI.

The importance of a preventing fluid overload was further highlighted in this study.

LIMITATIONS

This study is limited by the fact that it was a single center, retrospective study in a dedicated medical ICU. A further limitation is relying on creatinine as a marker for disease progression in this age group where a baseline creatinine was not always available and where CKD was prevalent. Our initial criteria of a raised creatinine above 140 μmol/L may have missed some patients who were sarcopenic [23].

A multicenter prospective study should be performed in medical and surgical ICUs to further evaluate the prognostic factors affecting the very elderly patients. A study using creatinine trajectory may also be warranted.

CONCLUSIONS

AKI in VOP who survived the first 24 hours of ICU admission is associated with a significantly increased mortality in comparison to age- and sex-matched controls. The most important markers of

mortality include positive fluid balance and APACHE II. Despite the higher mortality associated with AKI, 63% of the patients who survived were discharged home. This is an important consideration when allocating ICU beds to the aging population.

Correspondence

Dr. M. Romain
Dept. of Medical Intensive Care, Hadassah Medical Organization
and Faculty of Medicine, Hebrew University of Jerusalem 91120, Israel
Email: marcro@hadassah.org.il

References

1. Hoste EAJ, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015; 41 (8): 1411-23.
2. Chronopoulos A, Rosner MH, Cruz DN, Ronco C. Acute kidney injury in elderly intensive care patients: a review. *Intensive Care Med* 2010; 36 (9): 1454-64.
3. Flaatten H, de Lange DW, Artigas A, Bin D, Moreno R, Christensen S, Joynt GM, Bagshaw SM, Sprung CL, Benoit D, Soares M, Guidet B. The status of intensive care medicine research and a future agenda for very old patients in the ICU. *Intensive Care Med* 2017; 43 (9): 1319-28.
4. Sprung CL, Artigas A, Kesecioglu J, et al. The Eldicus prospective, observational study of triage decision making in European intensive care units. Part II: intensive care benefit for the elderly. *Crit Care Med* 2012; 40 (1): 132-8.
5. Rewa O, Bagshaw SM. Acute kidney injury-epidemiology, outcomes and economics. *Nat Rev Nephrol* 2014; 10 (4): 193-207.
6. Kon AA, Shepard EK, Sederstrom NO, et al. Defining Futile and Potentially Inappropriate Interventions: a policy statement from the Society of Critical Care Medicine Ethics Committee. *Crit Care Med* 2016; 44 (9): 1769-74.
7. Sebastiani P, Thyagarajan B, Sun F, et al. Biomarker signatures of aging. *Aging Cell* 2017; 16 (2): 329-38.
8. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2 (1): 1-138.
9. Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018; 14 (10): 607-25.
10. Porter CJ, Moppett IK, Juurlink I, Nightingale J, Moran CG, Devonald MAJ. Acute and chronic kidney disease in elderly patients with hip fracture: prevalence, risk factors and outcome with development and validation of a risk prediction model for acute kidney injury. *BMC Nephrol* 2017; 18 (1): 1-11.
11. O'Sullivan ED, Hughes J, Ferenbach DA. Renal aging: Causes and consequences. *J Am Soc Nephrol* 2017; 28 (2): 407-20.
12. Guidet B, de Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. *Intensive Care Med* 2020; 46 (1): 57-69.
13. Fortrie G, Stads S, Aarnoudse AJH, Zietse R, Betjes MG. Long-term sequelae of severe acute kidney injury in the critically Ill patient without comorbidity: a retrospective cohort study. *PLoS One* 2015; 10 (3): 1-12.
14. Funk I, Seibert E, Markau S, Girndt M. Clinical course of acute kidney injury in elderly individuals above 80 years. *Kidney Blood Press Res* 2016; 41 (6): 947-55.
15. Li Q, Zhao M, Zhou F. Hospital-acquired acute kidney injury in very elderly men: clinical characteristics and short-term outcomes. *Aging Clin Exp Res* 2020; 32 (6): 1121-8.
16. Berar Yanay N, Abu Arisha M, Berkowitz Y. Acute kidney injury in patients undergoing hip fracture surgery. *IMAJ* 2021; 23: 815-8.
17. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 2009; 20 (1): 223-8.
18. Fortrie G, De Geus HRH, Betjes MGH. The aftermath of acute kidney injury: A narrative review of long-term mortality and renal function. *Crit Care* 2019; 23 (1): 1-11.
19. Zhang J, Crichton S, Dixon A, Seylanova N, Peng ZY, Ostermann M. Cumulative fluid accumulation is associated with the development of acute kidney injury and non-recovery of renal function: a retrospective analysis. *Crit Care* 2019; 23 (1): 1-10.
20. Trejnowska E, Skoczyński S, Armatowicz P, et al. The importance of fluid balance in critically ill patients - a retrospective observational study. *Kardiol Pol* 2019; 1147-54.
21. Margolis G, Kofman N, Gal-Oz A, Arbel Y, Khoury S, Keren G, Shacham Y. Relation of positive fluid balance to the severity of renal impairment and recovery among ST elevation myocardial infarction complicated by cardiogenic shock. *J Crit Care* 2017; 40: 184-8.
22. Druml W, Lax F, Grimm G, Schneeweiss B, Lenz K, Laggner AN. Acute renal failure in the elderly 1975-1990. *Clin Nephrol* 1994; 41 (6): 342-9.
23. Kashani K, Rosner MH, Ostermann M. Creatinine: From physiology to clinical application. *Eur J Intern Med* 2020; 72: 9-14.

Who is content with nothing possesses all things.
Nicolas Boileau-Despreaux (1636–1711), French poet and critic

Capsule

Driving glioblastoma progression

Glioblastoma is a highly aggressive primary brain tumor that is initially treated by a combination of surgery, radiotherapy, and chemotherapy. However, the tumors often recur, and survival rates are poor. **Hoogstrate** and colleagues performed RNA sequencing on matched primary and recurrent glioblastoma resections to investigate progression and found that tumor cell content was reduced between primary and recurrent samples. This effect correlated with increased infiltration of tumor-associated macrophages and $CD4^+$ T cells. The authors found that after correcting for reduced tumor cell content the expression of 722 genes was altered between primary and recurrent samples. Surprisingly, none of these were genes associated with glioblastoma tumorigenesis and progression. Clustering gene expression data revealed higher proportions of neurons and oligodendrocytes and fewer endothelial cells at recurrence, indicating that the tumor microenvironment drives glioblastoma progression.

Cancer Cell 2023; 10.1016/j.ccell.2023.02.019
Eitan Israeli