GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 18 - 22, 2022

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Is Race a Necessary Factor for eGFR Calculation?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

New Creatinine-Cystatin C-Based Equations to Estimate GFR without Race

Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med.* 2021; 385(19):1737–1749. doi:10.1056/NEJMoa2102953

KEY TAKEAWAY: New eGFR equations that use both creatinine and cystatin C, and omit race, are more accurate with less differences between non-Black and Black persons than new equations using creatinine or cystatin alone.

STUDY DESIGN: Retrospective cohort review

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Race along with age, sex, and gender continues to be used in current estimated glomerular filtration equations despite its limitations as a social construct allowing for possible systemic racism in medicine.

PATIENTS: US adults who are ambulatory without comorbidities requiring hospitalization

INTERVENTION: New eGFR equations that use a White race variable for everyone or remove race totally as a factor

CONTROL: Use of current eGFR equations that include Black race variable for eGFR calculation

OUTCOME: Bias within race groups

Secondary Outcomes: Prevalence of CKD and GFR stages

METHODS (BRIEF DESCRIPTION):

- Four new eGFR equations were generated using 10 prior studies with 8,254 participants (32% Black) for eGFR creatinine equation and 13 studies with 5,352 participants (40% Black) for eGFRcr-cys.
- These four equations included two that removed the Black coefficient (Age, Sex, Race-Nonblack [ASR-N]) and two that removed race as an explanatory variable (Age, Sex [AS]).
- These equations were then compared to three current eGFR equations using a separate validation data set of 12 studies (4,050 participants) with known measured GFR.
- Accuracy was then assessed via bias, sensitivity, and differential bias within race groups.
- Prevalence of CKD and GFR stages in US adults were estimated using the equations.

INTERVENTION (# IN THE GROUP): 4,050

COMPARISON (# IN THE GROUP): 4,050

FOLLOW UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- CR based equations eGFR:
  - Current eGFRcr (ASR) overestimated GFR in Blacks by -3.7 mL/min (95% CI, −1.8 to −5.4), marginally overestimated GFR in non-Blacks by -0.5 mL/min (95% CI, −0.9 to −0.0).
  - New eGFRcr (AS) underestimated GFR in Blacks by 3.6 mL/min (95% CI, 1.8–5.5), overestimated GFR in non-Blacks by -3.9 mL/min (95% CI, −3.4 to −4.4).
  - New eGFRcr (ASR-NB) underestimated GFR in Blacks by 7.1 mL/min (95% CI, 5.9–8.8).
- CR-Cys based equations eGFR:
  - eGFRcr-csy (ASR) underestimated GFR in Blacks and non-Blacks by 2.5 mL/min (95% CI, 3.7–1.2) and 0.6 mL/min (95% CI, 0.9–0.2).
  - eGFRcr-cys (ASR-NB) overestimated GFR in Blacks by -3.4 mL/min (95% CI, −1.5 to −4.5) and underestimated GFR in non-Blacks by 0.6 mL/min (95% CI, 0.9–0.2).
  - eGFRcr-csy (AS) overestimated GFR in Blacks by −0.1 mL/min (95% CI, −0.9 to 1.6) and underestimated in non-Blacks by 2.9 mL/min (95% CI, 3.3–2.5).
- Csy-based equations eGFRcsy(AS) had the least amount of bias between Blacks and non-Blacks, however, had the least amount of agreement within 30% of the GFR and GFR categories.

Secondary Outcome–

- New cr-cys equations had less effect on estimation of prevalence of CKD than new creatinine-based equations alone and generally had less movement across GFR thresholds.

*All GFR units reported as ml per minute per 1.73 m^2 of body-surface area

LIMITATIONS:

- This study was limited by race being categorized into only two groups.
- The studies used to develop the equations and studies used for verification had significantly different percentages of Black participants leading to less precise estimations of accuracy.
- The study did not include participants with other comorbidities limiting application in the

acute setting.

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The Effect of COVID-19 on Our Homeless Populations

Characteristics of COVID-19 in Homeless Shelters : A Community-Based Surveillance Study

Rogers JH, Link AC, McCulloch D, et al. Characteristics of COVID-19 in Homeless Shelters : A Community-Based Surveillance Study. *Ann Intern Med*. 2021; 174(1):42–49. doi:10.7326/M20-3799

KEY TAKEAWAY: In the homeless population most positive SARS-CoV-2 cases were found during surge testing rather than routine surveillance and most cases were usually greater than 60 years old and sleeping in communal spaces.

STUDY DESIGN: Cross- sectional, community-based surveillance study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The United States homeless population is greater than 560,000. These individuals have a higher rate of morbidity and mortality than the general populace due to respiratory pathogens which are more easily transmissible in the crowded facilities with shared hygiene spaces. Additionally, homeless populations may have more difficulty accessing health care services.

PATIENTS: Homeless shelter staff and shelter residents in King County, Washington

INTERVENTION: Contact tracing during community surges of the infection and routine surveillance in 14 homeless shelters

CONTROL: Rates of SARS-CoV-2 infection in homeless shelters across a metropolitan region were compared

OUTCOME: SARS-CoV-2 infection as detected by nasal swab with or without symptoms

METHODS (BRIEF DESCRIPTION):

- Patients were greater than 3 months old, living at one of 14 homeless shelters in King County, WA, and were experiencing 2 or more acute respiratory infection symptoms.
- Initially, from January 1 to March 31, 2020, participates were evaluated monthly and were eligible to participate with or without symptoms for SARS-CoV-2. Only shelter residents were eligible for testing.
- From April 1 to April 24, 2020, surge testing was initiated in addition to routine surveillance three times a week for both shelter residents and staff.
- Patients were evaluated by an electronic questionnaire for documenting symptoms and while initially study staff collected mid-nasal swabs, the study ended with participants doing their own nasal swab under supervision.

INTERVENTION (# IN THE GROUP): 1,434

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW UP PERIOD: No longitudinal follow up

RESULTS:

- Of the 1,434 encounters with participants, 29 were positive for SARS-CoV-2. Positive rates were similar among shelter staff (2.5%) and residents (2.0%).
- The positivity rate of the study was lower than the rate found in the community reflected by the 8.8% rate seen at the University of Washington clinical laboratory.
- Eight encounters were symptomatic (28%), mean Ct value 28 (SD, 5.0); 21 had no symptoms (72% [LI, 53% to 87%]), mean Ct value 30 (SD, 6.1).
- The majority of positive cases were found while surge testing events were conducted (n=21, 72%). Routine surveillance yielded a lower number of positive cases (n=8, 28%).
- Positive cases of SARS-CoV-2 were found at five shelters. Most positive cases were found at shelters caring for older male residents, day center services that were shared, showering facilities, and in staff that rotated between shelter sites.

LIMITATIONS:

- Participation was voluntary in nature, so there may have been selection bias.
- Poor trust in health care may have led to greater asymptomatic cases being detected during surge testing due to shelter staff encouraging participation.
- The relatively small number of positive cases limits the ability to evaluate sleeping arrangements and this factor's contribution to the spread of the SARS-CoV-2.
- Later in the study, self-swabbing techniques of the nasal were used, and the reliability of this method is not assured.

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Exercise: It Can Save Your Life

Estimated Number of Deaths Prevented Through Increased Physical Activity Among US Adults

Saint-Maurice PF, Graubard BI, Troiano RP, et al. Estimated Number of Deaths Prevented Through Increased Physical Activity Among US Adults. *JAMA Intern Med*. 2022; 182(3):349–352. doi:10.1001/jamainternmed.2021.7755

KEY TAKEAWAY: Modest increases in daily moderate to vigorous activity is associated with reduced all-cause mortality.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Exercise is commonly recommended by physicians and professional guidelines as a key component of a healthy lifestyle and a tool to promote longevity. Previous studies have been limited in their ability to estimate impact on mortality by self-reported exercise data and small sample sizes.

PATIENTS: Adults between 40–85 years old

INTERVENTION: Daily moderate to vigorous activity

CONTROL: Not applicable

OUTCOME: Mortality

METHODS (BRIEF DESCRIPTION):

- NHANES survey participants six years or older were asked to wear an accelerometer for 7 days.
- Accelerometer data and all-cause mortality (10-year mean follow up period) from NHANES survey participants aged 40-85 years old was analyzed.
- Moderate to vigorous physical activity levels of participants were stratified into eight activity categories and actual mortality of category members were compared to adjusted population attributable fraction based on US actual death data from 2003 for adults aged 40-84 years old.
- Hazard ratios were calculated used Cox proportional hazard regression models.

INTERVENTION (# IN THE GROUP): 4,840

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Mean time of 10 years

RESULTS:

Addition of 10 or more minutes of moderate to vigorous physical activity was associated with the prevention of:

- 8% of deaths (95% CI, 6.0–10) per year for men
- 5.9% of deaths (95% CI, 2.0–9.8) among women
- 4.8% of deaths (95% CI, 0.0–11) among Mexican Americans
- 6.1% of deaths (95% CI, 2.2–10) for non-Hispanic Blacks
- 7.3% of deaths (95% CI, 5.3–9.3) for non-Hispanic Whites

LIMITATIONS:

- Mortality impact was based on the adjusted population attributable fraction of deaths multiplied by the US population deaths in 2003 and not on comparison to a control cohort.
- NHANES study population is a representative survey sample with no randomization.
- Length of exercise exposure measurement with accelerometer only seven days with 10-year average follow up.
- Cohort study design limits assessment of causality.

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The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

Labetalol Has Slight Advantages Over Other Oral Antihypertensives in Pregnancy Hypertensive Disorders

Oral Antihypertensives for Nonsevere Pregnancy Hypertension: Systematic Review, Network Meta- and Trial Sequential Analyses

Bone JN, Sandhu A, Abalos ED, et al. Oral Antihypertensives for Nonsevere Pregnancy Hypertension: Systematic Review, Network Meta- and Trial Sequential Analyses. *Hypertension.* 2022; 79(3):614–628. doi:10.1161/HYPERTENSIONAHA.121.18415

KEY TAKEAWAY: Antihypertensives used to treat non-severe hypertension in pregnancy decrease the incidence of severe hypertension. However, only labetalol decreases the risk of preeclampsia, proteinuria, and perinatal death.

STUDY DESIGN: Meta-analysis of 61 randomized trials (N=6,923)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Hypertension in pregnancy is an important source of maternal and neonatal morbidity and mortality with severe hypertension further increasing these risks. With increasing national and international advocacy to treat non-severe hypertension in pregnancy, determining which medications provide superior outcomes would be beneficial to know when choosing an antihypertensive option.

PATIENTS: Pregnant women with non-severe hypertension on antihypertensive medications

INTERVENTION: Labetalol, methyldopa, calcium channel blockers (CCBs), mixed/multi-drug therapy

CONTROL: Placebo/no therapy, or a different antihypertensive

OUTCOME: Severe hypertension, proteinuria or preeclampsia, adverse neonatal outcomes

Secondary Outcomes: Need for additional antihypertensive, changed/stopped drug, placental abruption, cesarean delivery

METHODS (BRIEF DESCRIPTION):

- Online databases were used to identify randomized trials of non-severe, maternal hypertension treated with antihypertensive medications.
- Definition of non-severe hypertension was systolic blood pressure 140–159 and diastolic blood pressure 90–109.
- Patients had to be on treatment for greater than or equal to seven days.
- Comparison of head-to-head trials of antihypertensives to no treatment/placebo and other antihypertensives was done using Bayesian meta-analysis.
- Network meta-analysis was used when no head-to-head trials were available.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Pregnancy duration and neonatal period

RESULTS:

Primary Outcome –

- Commonly used antihypertensives decreased the rate of severe hypertension compared to no therapy/placebo (32 trials; N=3,811).
  - Labetalol: 69% reduction (OR 0.31; 95% CI, 0.18–0.51)
  - Multi-drug therapy: 68% reduction (OR 0.32; 95% CI, 0.12–0.80)
  - Methyldopa: 40% reduction (OR 0.60; 95% CI, 0.39–0.91)
  - CCBs: 41% reduction (OR 0.59; 0.95% CI, 0.37–0.89)
- Labetalol decreased the incidence of:
  - Proteinuria and preeclampsia (32 trials; N=4,662)
    - 27% reduction compared to no treatment/ placebo (OR 0.73; 95% CI, 0.53–0.98).
    - 34% reduction compared to methyldopa (OR 0.66; 95% CI, 0.44–0.99).
    - 34% reduction compared to CCBs (OR 0.66; 95% CI, 0.41–0.96).
  - Perinatal death (44 trials; N=5,051)
    - 46% reduction compared to no therapy/placebo (OR 0.54; 95% CI, 0.30–0.98).

Secondary Outcome –

- Several antihypertensives decreased the need for additional medication compared to no therapy/placebo (23 trials; N=2,927).
  - Multidrug therapy: 71% decrease (OR 0.29; 95% CI, 0.11–0.66)
  - Labetalol: 62% decrease (OR 0.38; 95% CI, 0.21–0.66)
  - CCBs: 56% decrease (OR 0.44; 95% CI, 0.22–0.88)

There was no significant difference in other adverse neonatal or other secondary outcomes.

LIMITATIONS:

- Retrospective methodology was used and constrained by available literature, much of which was more than 20 years old.
- Many indirect comparisons were used, thus there is a risk that significant results were obtained by chance.
- Prohibitive sample sizes are estimated to be needed to obtain definitive evidence for even the most common endpoints such as severe hypertension.

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