Longitudinal Association of a Medication Risk Score With Mortality Among Ambulatory Patients Acquired Through Electronic Health Record Data

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The use of electronic health records allows for the application of a novel medication risk score for the rapid identification of ambulatory patients at risk of adverse drug events. We sought to examine the longitudinal association of medication risk score with mortality. This retrospective cohort study included patients whose data were available through electronic health records from multiple health care organizations in the United States that provided data as part of a Patient Safety Organization. Patients were included if they had ≥1 visit and ≥1 medication in their record between January 1, 2011, to June 30, 2017. Cox proportional hazards regression was used to examine the association between continuous and categorized medication risk score with all-cause mortality. Among 427,103 patients, the median age was 50 years (interquartile range, 29–64 years); 61% were female; 50% were White, 11% were Black, and 38% were Hispanic; and 6,873 had a death date recorded. Patients 30 to 49 years old had the highest hazard ratios (HRs), followed by the 50- to 64-year-olds and lastly those 65 years or older. Controlling for all covariates, 30- to 49-year-olds with a medication risk score of 20 to 30 (versus <10) had a 604% increase in the hazard of death. We conclude that pharmaceutical interventions among those with elevated scores could harm.5,6 This results both from the high number of medications prescribed7 and the complex processes involved between clinical decision making, communication to the pharmacy, dispensing, and actual use.8–10 The widespread adoption of electronic health records (EHRs) has been considered the primary driver to more adequately address medication risk.11,12 Electronic health records have improved legibility issues and perhaps dosing and disease–drug and drug interactions13–15; however, medication safety, and the prevention of medication errors and subsequent adverse drug events (ADEs) continues to be a significant global public health challenge.16–18 In the United States, it is estimated that ADEs account for approximately 3.5 million physician office visits, 1 million emergency department (ED) visits, and 125,000 hospital admissions annually.19–21 Prevention of ADEs is a key patient safety priority of many national health care-regulating agencies,22–24 and evidence-based tools for the early identification of patients at risk of ADEs are needed to significantly improve medication safety.25 The increase in the average number of medications used by a single individual has highlighted the need to develop new methods of addressing medication risk.26–28 As process errors in the order, dispensing, and use chain improve, more complex drug and disease interactions can be prioritized to reduce harm from therapeutic medication use.29–31 Multimorbidity is associated with higher complexity of medication regimens and a greater chance that complex interactions between medications and an individual’s conditions may lead to harm.32–34 In an attempt to manage medication safety, many larger health care systems have implemented Medication Therapy Management (MTM) programs, and the U.S. Centers for Medicare & Medicaid Services requires that MTM programs be included as part of the provision of Part D benefits.35–37 These programs typically identify individuals based on the number of drugs they are using, particular disease states (e.g., diabetes mellitus or hypertension) and/or an event (e.g., hospitalization).38–40 A clinical pharmacist is then needed to review the medication regimens and to talk with the patients to determine if adjustments are warranted. This process relies heavily on the pharmacists’ clinical knowledge of the various conditions encountered in each patient. More advanced techniques are needed as knowledge increases regarding medication metabolism, side effects, and interactions with developed...
and fixed (i.e., genetic) patient characteristics. In 2017, the U.S. Centers for Medicare & Medicaid Services introduced a Part D Enhanced MTM 5-year pilot program where advanced clinical decision support systems and pharmacist-directed interventions are used.\textsuperscript{36} Computer-based risk algorithms hold the potential to efficiently and effectively support medication safety programs.\textsuperscript{23,37}

Tabula Rasa HealthCare has developed a proprietary advanced clinical decision support system and medication risk score (MRS), which incorporates a series of algorithms that calculate an overall score, as well as subcomponent scores on sedation burden,\textsuperscript{38,40} anticholinergic cognitive burden,\textsuperscript{41} a competitive CYP450 drug interaction burden,\textsuperscript{24} drug regimen relative odds ratio for ADE using the Food and Drug Administration adverse event reporting system,\textsuperscript{38} and a drug-induced risk of creating or worsening a prolonged QT cardiac repolarization interval.\textsuperscript{37,2,43} An observational study using claims data among participants of the Program of All-Inclusive Care for the Elderly found the total MRS to be positively correlated with increased ADEs, health care utilization, hospitalization, ED visits, and hospital length of stay.\textsuperscript{44} However, this study did not assess an independent risk of death and did not include other clinical variables that may have a strong impact on the overall score.

The current observational study was conducted as part of the safety work of the DARTNet Institute subcomponent Patient Safety Organization (PSO).\textsuperscript{45} We hypothesized that the MRS was an independent predictor of death among a cohort of ambulatory patients obtained through EHR data. In comparison to claims data, EHRs include clinical variables (e.g., estimated glomerular filtration rate [eGFR], blood pressure [BP] values, and laboratory measured electrolyte levels), allowing EHR-based algorithms to have the potential for greater dissemination and more rapid response to medication changes, which may improve health outcomes and reduce health care costs.

\section*{METHODS}

\subsection*{Study Population and Eligibility}

This retrospective cohort study uses EHR data from multiple U.S. health care organizations that provide data in partnership with DARTNet’s PSO. This study includes community-living, ambulatory patients 5 years and older who had data present between January 1, 2011, and June 30, 2017, and who had at least one medication present (i.e., prescribed or added during medication reconciliation) within the study period.

\subsection*{Data Measures}

The dependent variable of interest is death from any cause as determined by the presence of a date of death within the patient’s EHR record. The main independent variable of interest is MRS, which ranges from 0 to 53, with a higher score indicating a higher risk of ADEs due to a particular medication regimen, including anticholinergic burden, sedating effects, risk of QT-interval prolongation, and the competitive inhibition on certain cytochrome P450 isozymes.\textsuperscript{42,46} Medication risk score was also categorized for analysis (<10, 11–14, 15–19, 20–30, >30). Details regarding the calculation of the MRS and its components have been published elsewhere.\textsuperscript{37,42,46} The calculation of the MRS considers all prescribed medications and patients’ characteristics during a given period of time. Data were extracted from EHR records and compiled into eras (i.e., time frames) to account for the dynamic nature of the MRS. An era is defined by current medication exposures (including strength); laboratory results categorized as low, normal, or high (calcium (<8.5, 8.5–10.5, and >10.5 mg/dL), potassium (<3.5, 3.5–5, and >5 mg/dL), magnesium (<1.5, 1.5–2.5, and >2.5 mg/dL); and selected conditions (i.e., end-stage renal disease, atrial fibrillation, end-stage liver disease, atherosclerotic cardiovascular disease, heart failure, cardiomyopathy, prolonged QT interval, sick sinus syndrome). A change in any of these factors closes the current era and commences a new era, as long as there continues to be at least one medication exposure.

Each patient-era includes covariates measured during that era including the following: sociodemographic factors (i.e., age, sex, and race/ethnicity as identified in the EHR, categorized as White, non-Hispanic or unknown ethnicity; Black, non-Hispanic or unknown ethnicity; Hispanic/Latino; other/mixed non-Hispanic; and unknown/missing both race and ethnicity), health-related factors (body mass index [BMI], BP, kidney function based on eGFR, chronic kidney disease, and liver disease), and total days in the era and total medications listed in the EHR during that particular era. Age was divided into quartiles (ages <30, 30–49, 50–64, and ≥65 years); systolic and diastolic BP values were limited to clinically plausible ranges of 50 to 250 and 0 to 200 mm Hg, respectively, and were categorized as normal (systolic BP <120 mm Hg or diastolic BP <80 mm Hg) or elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg); BMI values were limited to 12 to 70 kg/m² and were categorized for adults into underweight (<18.5 kg/m²), normal (18.5–24 kg/m²), overweight (25–30 kg/m²), or obese (>30 kg/m²); eGFR (in mL min⁻¹ 1.73 m²) was categorized into stages of chronic kidney disease (stages 1–2, ≥60; stage 3a, 45–59; stage 3b, 30–44; stages 4–5, <30); and liver disease was categorized as no liver disease, chronic liver disease, or end-stage liver disease based on International Classification of Diseases, Tenth Revision diagnoses. All outlier values were set to missing for analyses. Finally, the Charlson-Deyo Score, calculated from the sum of scores for each comorbid condition listed in the Charlson Comorbidity Score Mapping Table, was used to account for multimorbidity.\textsuperscript{47,48}

\subsection*{Statistical Analysis}

Descriptive statistics were calculated using mean and SD, or median and interquartile range (IQR) for continuous measures; and frequency and percentage for categorical measures. Differences by mortality status were examined using χ² tests for categorical measures and t tests for continuous measures.\textsuperscript{49} Cox proportional hazards regression modeling with time-varying covariates was used to examine the unadjusted and multivariable association of MRS with all-cause mortality and to account for within-person changes over time and eras that may occur among all variables. Proportional hazards assumptions were verified by examining Schoenfeld residuals and were determined to have been met.\textsuperscript{49} The primary outcome was number of days from the start date of an era to the date of death if it occurred during a particular era. Patients were censored at the end of each era if they did not have a date of death ending that era. Covariates were adjusted for using a stepwise approach to determine their effect on the association of MRS with death, where variables were considered to be a confounder of this association if they changed the point estimate of the main association >10% when included into the multivariable model. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported to show strength and direction of these associations. Data were analyzed using SAS 9.4 (Cary, North Carolina), and a level of P < 0.05 was used to determine statistical significance.

\section*{RESULTS}

A total of 427,103 patients with at least one visit to a qualifying medical practice and at least one medication record during the study period were eligible for MRS calculation. A total of 6873 patients (1.6%) died by the end of the study period. The median
age at baseline was 50 years (IQR, 29–64 years), and 25% were younger than 30 years (with 14.7% being 5–18 years old), 24% were 30 to 49 years old, 26% were 50 to 64 years old, and 24.5% were 65 years and older (Table 1). More than half were female (61%); almost 50% were White, 11% were Black, and almost 38% were Hispanic. Over the entire study period, there were a total of 2,491,399 eras present for analysis, with a median number of eras per patient of 12 (IQR, 5–25; range, 1–236) and a median number of days per era of 62 (IQR, 14–189; range, 1–2372).

Compared with patients who did not have a date of death present within their EHR, those who did were significantly more likely to be older at baseline (74 versus 49 years; \( P < 0.01 \)), male (52.3% versus 38.7%; \( P < 0.01 \)), and White (57.2% versus 49.4%; \( P < 0.01 \)) (Table 1). Over the entire study period, they had a significantly higher median MRS (9 versus 5; \( P < 0.01 \)), higher median number of medications (7 versus 4; \( P < 0.01 \)), lower average BMI (28.7 versus 29.4 kg/m²; \( P < 0.01 \)), lower average eGFR (58.2 versus 78.1 mL min⁻¹ 1.73 m⁻²; \( P < 0.01 \)), and higher average Charlson-Deyo score (4 versus 2; \( P < 0.01 \)). Furthermore, those who died had a significantly greater median number of total eras (22 versus 12; \( P < 0.01 \)), with lower median days per era (36 versus 63; \( P < 0.01 \)) and significantly greater average number of days in the study period (1654 versus 1530; \( P < 0.01 \)).

Table 2 displays the results of age-stratified unadjusted Cox proportional hazards regression models examining the association

### TABLE 1. Bivariate Analysis of Patient Characteristics by Overall Mortality Status Among Ambulatory Patients in the United States, 2011 to 2017

| Characteristics, Baseline | Total (n = 427,103)* | Alive (n = 420,230) | Deceased (n = 6873) | \( P \) |
|---------------------------|---------------------|---------------------|---------------------|------|
| Age, y                    |                     |                     |                     |      |
| Median (IQR)              | 50 (29–64)          | 49 (29–64)          | 74 (65–82)          | <0.0001 |
| n (%)                     |                    |                    |                    |      |
| <30                       | 108,074 (25.3)      | 107,991 (25.7)      | 83 (1.2)            | <0.0001 |
| 30–49                     | 102,997 (24.1)      | 102,688 (24.4)      | 309 (4.5)           |      |
| 50–64                     | 111,439 (26.1)      | 110,215 (26.2)      | 1224 (17.8)         |      |
| ≥65                       | 104,593 (24.5)      | 99,336 (23.6)       | 5257 (76.5)         |      |
| Sex, n (%)                |                     |                     |                    |      |
| Male                      | 166,299 (38.9)      | 162,702 (38.7)      | 3597 (52.3)         | <0.0001 |
| Female                    | 260,804 (61.1)      | 257,528 (61.3)      | 3276 (47.7)         |      |
| Race/ethnicity, n (%)     |                     |                     |                    |      |
| White, non-Hispanic or unknown ethnicity | 211,331 (49.5) | 207,401 (49.4) | 3390 (57.2) | <0.0001 |
| Black, non-Hispanic or unknown ethnicity | 47,055 (11.0) | 46,482 (11.1) | 573 (8.3) |      |
| Hispanic/Latino           | 160,610 (37.6)      | 158,405 (37.7)      | 2205 (32.1)         |      |
| Other/mixed               | 2499 (0.6)          | 2467 (0.6)          | 32 (0.5)            |      |
| Unknown/missing both race and ethnicity | 5608 (1.3) | 5475 (1.3) | 133 (1.9) |      |

| Characteristics, All Eras | Total (n = 2,491,399) | Alive (n = 2,413,450) | Deceased (n = 77,949) | \( P \) |
|---------------------------|-----------------------|-----------------------|-----------------------|------|
| MRS                       | 5 (2–10)              | 5 (2–10)              | 9 (4–15)              | <0.0001 |
| n (%)                     | 1,795,027 (72.1)      | 1,754,167 (72.7)      | 40,860 (52.4)         | <0.0001 |
| 11–14                     | 384,085 (15.4)        | 367,159 (15.2)        | 16,926 (21.7)         | <0.0001 |
| 15–19                     | 190,017 (7.6)         | 179,370 (7.4)         | 10,647 (13.7)         |      |
| 20–30                     | 112,352 (4.5)         | 103,739 (4.3)         | 8613 (11.1)           |      |
| >30                       | 9918 (0.4)            | 9015 (0.37)           | 903 (1.2)             |      |
| Total medications, median (IQR) | 4 (2–8) | 4 (2–8) | 7 (4–11) | <0.0001 |
| BMI\(^1\) (n = 318,175), mean (SD), kg/m² | 29.4 (7.4) | 29.4 (7.4) | 28.7 (7.2) | <0.0001 |
| BP\(^1\) (n = 368,907), n (%) | 279,735 (79.6) | 289,251 (79.7) | 4502 (73.2) | <0.0001 |
| Normal                    | 75,154 (20.4)         | 73,502 (20.3)         | 1652 (26.8)           |      |
| Elevated                  | 2.0 (1.9)             | 2.0 (1.9)             | 4.0 (2.2)             | <0.0001 |
| eGFR (n = 348, 131), mean (SD), mL min⁻¹ 1.73 m⁻² | 77.3 (25.7) | 78.1 (25.5) | 58.2 (23.5) | <0.0001 |
| Charlson-Deyo Score, mean (SD) | 2.0 (1.9) | 2.0 (1.9) | 4.0 (2.2) | <0.0001 |
| Total eras per person, median (IQR) | 12 (5–25) | 12 (5–25) | 22 (11–37) | <0.0001 |
| Days per era, median (IQR) | 62 (14–189) | 63 (15–191) | 36 (11–107) | <0.0001 |
| Days in study per person, mean (SD) | 1639 (964–2,221) | 1530 (693.3) | 1654 (625.1) | <0.0001 |

*Total patients available for analysis unless otherwise indicated.

\(^1\)Limited to those 18 years or older.
of the continuous MRS, as well as MRS categorized into 5 groups, with all-cause mortality. Stratifying for age revealed that the hazard of death at any time point during the study varied by age group, with the highest HRs seen in the 30- to 49-year-old group. A 1-unit increase in MRS was associated with an 11% increase in the hazard of death among patients aged 30 to 49 years (HR, 1.12; 95% CI, 1.10–1.14). Examining the association of the categorized MRS with death, the highest HRs were seen among the 30- to 49-year-old age group, followed by the 50- to 64-year-old age group and lastly those 65 years or older. Those aged 30 to 49 years with an MRS of 20–30 had a 795% increase in the hazard of death compared to those with an MRS <10 (HR, 8.95; 95% CI, 5.90–13.58), whereas 50- to 64-year-olds had a 357% increase (HR, 4.57; 95% CI, 3.74–5.57) and ≥65 year-olds had an 149% increase (HR, 2.29; 95% CI, 2.29–2.71).

Table 3 displays the results of the multivariable Cox proportional hazards regression model controlling for Charlson-Deyo Score, sex, race/ethnicity, BMI, and eGFR showing the significance of the other covariates. Although Charlson-Deyo, sex, race/ethnicity BMI, and eGFR are all associated with death, none were found to have an HR higher than MRS. Moreover, the addition of eGFR to the model further increased the strength of the HR for some categories of MRS and age groups. Total medications, BP, total eras per person, days per era, and total days in the study were not found to change the measure of association more than 10% in multivariable modeling and were therefore not included in the final model. Among patients aged 30 to 49 years with an MRS of 20–30, the HR went from 6.27 (95% CI, 3.81–10.33; Online Supplemental Table, http://links.lww.com/JPS/A385) to 7.04 (95% CI, 3.86–12.85); and among those aged 50 to 64 years with an MRS >30, the HR

| MRS | All Patients, HR (95% CI) | Ages <30 y, HR (95% CI) | Ages 30–49 y, HR (95% CI) | Ages 50–64 y, HR (95% CI) | Ages ≥65 y, HR (95% CI) |
|-----|--------------------------|-------------------------|--------------------------|--------------------------|-------------------------|
| MRS (1 unit) | 1.05 (1.04–1.05) | 1.09 (1.05–1.14) | 1.12 (1.10–1.14) | 1.08 (1.08–1.09) | 1.05 (1.05–1.06) |
| <10 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 10–14 | 3.00 (2.83–3.19) | 2.94 (1.46–5.92) | 2.66 (1.90–3.73) | 2.14 (1.83–2.51) | 1.65 (1.55–1.77) |
| 15–19 | 4.08 (3.81–4.38) | 4.87 (1.77–13.42) | 4.99 (3.39–7.35) | 2.92 (2.42–3.52) | 1.96 (1.81–2.11) |
| 20–30 | 5.70 (5.28–6.15) | — | 8.95 (5.90–13.58) | 4.57 (3.74–5.57) | 2.49 (2.29–2.71) |
| >30 | 7.65 (6.32–9.26) | — | 11.72 (2.90–47.39) | 4.86 (2.73–8.63) | 3.20 (2.61–3.92) |

*Outcome of death was rare in the <30-year age group for MRS categories 20–30 (n = 9) and >30 (n = 0), and therefore, the point estimate could not be calculated.

| MRS* | All Patients, HR (95% CI) | Ages <30 y, HR (95% CI) | Ages 30–49 y, HR (95% CI) | Ages 50–64 y, HR (95% CI) | Ages ≥65 y, HR (95% CI) |
|------|--------------------------|-------------------------|--------------------------|--------------------------|-------------------------|
| MRS (1 unit) | 1.05 (1.04–1.05) | 1.09 (1.05–1.14) | 1.12 (1.10–1.14) | 1.08 (1.08–1.09) | 1.05 (1.05–1.06) |
| <10 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 10–14 | 1.65 (1.52–1.79) | 2.83 (0.92–8.71) | 2.09 (1.27–3.44) | 1.76 (1.41–2.20) | 1.50 (1.37–1.64) |
| 15–19 | 1.81 (1.65–2.00) | 8.57 (2.74–26.81) | 3.35 (1.86–6.06) | 2.28 (1.77–2.95) | 1.57 (1.41–1.74) |
| 20–30 | 2.25 (2.03–2.49) | — | 7.04 (3.86–12.85) | 3.54 (2.74–4.63) | 1.87 (1.67–2.09) |
| >30 | 2.58 (2.06–3.25) | — | 7.83 (1.07–57.21) | 4.95 (2.60–9.41) | 2.42 (1.89–3.09) |
| Charlson-Deyo Score (1 unit) | 1.38 (1.37–1.39) | 1.45 (1.19–1.78) | 1.41 (1.29–1.55) | 1.42 (1.37–1.46) | 1.34 (1.33–1.36) |
| Sex | | | | | |
| Female | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Male | 1.32 (1.24–1.41) | 1.33 (0.57–3.12) | 3.03 (2.04–4.49) | 1.58 (1.33–1.88) | 1.27 (1.19–1.37) |
| Race/ethnicity, n (%) | | | | | |
| White, non-Hispanic or unknown ethnicity | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Black, non-Hispanic or unknown ethnicity | 0.91 (0.79–1.05) | — | 1.32 (0.69–2.52) | 0.88 (0.63–1.23) | 0.95 (0.80–1.12) |
| Hispanic/Latino | 0.90 (0.73–1.10) | — | 1.29 (0.47–3.59) | 1.52 (1.02–2.26) | 0.79 (0.62–1.01) |
| Other/mixed | 1.64 (1.37–1.98) | 3.31 (0.71–15.32) | 3.22 (1.67–6.20) | 1.15 (0.66–2.00) | 1.66 (1.35–2.05) |
| Unknown/missing both race and ethnicity | 1.26 (1.17–1.35) | 0.84 (0.34–2.06) | 0.91 (0.57–1.44) | 1.05 (0.86–1.29) | 1.34 (1.24–1.45) |
| BMI | 0.96 (0.95–0.96) | 0.96 (0.91–1.02) | 1.00 (0.98–1.03) | 0.97 (0.96–0.98) | 0.95 (0.95–0.96) |
| eGFR | 0.99 (0.98–0.99) | 1.01 (1.00–1.02) | 0.99 (0.99–1.00) | 0.99 (0.99–0.99) | 0.99 (0.98–0.99) |

*Outcome of death was rare in the <30-years age group for MRS categories 20–30 (n = 9) and >30 (n = 0), and therefore, the point estimate could not be calculated.
went from 4.09 (95% CI, 2.24–7.48; Online Supplemental Table, http://links.lww.com/JPS/A385) to 4.95 (95% CI, 2.60–9.41).
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