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LITERATURE REVIEW

JIM Reading List

Our Literature Review section continues with another installment of summaries from the medical literature. Our authors have found recent articles that have direct relevance to the practice of insurance medicine. The intent of the reading list is to provide the highlights of articles, not an in-depth analysis. Contributions to the reading list are invited. Please forward your citation and summary to Ted Gossard, MD or Stephanie Hrisko, MD, Associate Editors, Literature Review at GOSSAT2@nationwide.com or stephaniehrisko@thecasongroup.com. We will acknowledge all contributors in each issue's installment.

CARDIOLOGY

1. *Bin Abdul Jabbar A, Mansoor T, Osborne J, et al. Trends in obesity and heart failure-related mortality in middle-aged and young adult populations of the United States, 1999–2022.* BMC Cardiovasc Disord. *2025;25:601*. doi:10.1186/s12872-025-05029-4

The findings of a sustained increase in obesity-associated heart failure (HF) mortality in middle-aged and younger adults over the past two decades are relevant to life insurance risk assessment, underscoring the need to systematically consider obesity and its long-term impact on mortality.

This retrospective observational study analyzed national mortality trends related to HF and obesity among US adults aged 25 to 64 using CDC WONDER data from 1999 to 2022. A total of 58,290 deaths were attributed to both HF and obesity. The age-adjusted mortality rate (AAMR) for combined HF and obesity increased by 337%, from 0.72 per 100,000 in 1999 to a peak of 3.15 in 2021. Between 1999 and 2019, the AAMR rose by 154.17%, from 0.72 (95% CI: 0.68–0.77) to 1.83 (95% CI: 1.77–1.90), followed by a 72.13% increase to 3.15 (95% CI: 3.07–3.23) in 2021. The average annual percent change (AAPC) from 1999 to 2019 was 4.90 (95% CI: 4.57–5.33). Sensitivity analysis showed an acceleration in recent years, with APC rising from 6.0% (1999–2018) to 15.3% (2018–2022). COVID-19 contributed to 8.4% of HF and obesity deaths from 2020 to 2022.

HF-related mortality alone increased from an AAMR of 15.99 (95% CI: 15.79–16.20) in 1999 to 25.31 (95% CI: 25.09–25.53) in 2021. Obesity-related mortality rose by 161.66%, from 5.66 (95% CI: 5.54–5.79) in 1999 to 14.81 (95% CI: 14.63–14.99) in 2019, and more than doubled to 30.67 (95% CI: 30.41–30.93) in 2021. The proportion of HF deaths with obesity as a contributing cause increased from 4.5% in 1999 to 12.45% in 2021.

Sex-stratified analysis showed consistently higher AAMRs in men. From 1999 to 2019, the AAMR in men increased by 189%, from 0.77 (95% CI: 0.70–0.83) to 2.23 (95% CI: 2.13–2.32), with an AAPC of 5.64 (95% CI: 5.31–6.17). In women, the AAMR rose by 137.1%, from 0.62 (95% CI: 0.56–0.68) to 1.47 (95% CI: 1.39–1.54), with an AAPC of 4.46 (95% CI: 3.98–5.15). From 2019 to 2021, both sexes experienced similar increases of approximately 72%. Age-stratified analysis showed the greatest increase in crude mortality rate (CMR) from 1999 to 2019 in adults aged 55-64, rising 186.55% from 1.71 (95% CI: 1.55-1.88) to 4.90 (95% CI:

4.69-5.11). Adults aged 25-34 had the largest increase in CMR from 2019 to 2021, rising 89.66% from 0.29 (95% CI: 0.24-0.33) to 0.55 (95% CI: 0.48-0.62).

Smaller-scale disparities were observed across race, region, and geography. Non-Hispanic Black individuals had the highest mortality rates, while Hispanic individuals showed the greatest proportional increases. The South and rural areas experienced the steepest rises in mortality, and Oklahoma had the highest state-level rate in recent years. *Submitted by Marianne E. Cumming, MD*

2. *King SJ, Yuthok T, Bacong A, et al. Heart disease mortality in the United States, 1970 to 2022.* J Am Heart Assoc. *2025;14:e038644.* doi:10.1161/JAHA.124.038644

The authors analyzed CDC WONDER data for adults 25 years and older from 1970 to 2022 to evaluate trends in ischemic [acute myocardial infarction (AMI) and chronic ischemic heart disease (CIHD)] and other heart disease.* Joinpoint Regression was used to calculate percentage changes over time.

In 1970, there were 733,273 heart disease deaths (41% of the total deaths that year), of which 91% were ischemic (51% AMI, 46% CIHD) and 9% due to other heart disease. In 2022, there were 701,443 heart disease deaths (24% of total deaths) with 53% ischemic (29% AMI, 71% CIHD) and 47% due to other heart disease. The age-adjusted mortality for all heart disease deaths decreased 66% [761 to 258 per 100,000; average annual percentage change (AAPC) −2.0; 95% CI, −2.1 to −2.0] from 1970 to 2022. Mortality for ischemic heart disease decreased 81% (693 to 135 per 100,000; AAPC −3.1%; 95% CI, −3.2 to −3.1). The trends for age-adjusted AMI and CIHD mortality rates were as follows: AMI decreased 89% (354 to 40 per 100,000; AAPC −4.2%; 95% CI, −4.3 to −4.1) and CIHD decreased 71% (343 to 98 per 100,000; AAPC −2.5%; 95%CI, −2.6 to −2.4).

Conversely, the age-adjusted mortality from other heart diseases increased 81% (68 to 123 per 100,000; AAPC 1.2%; 95% CI, 1.1-1.2) with the greatest increases in arrhythmia (450%), heart failure (146%), and hypertensive heart disease (106%). The absolute rates remained lower than those of ischemic heart disease for these conditions at 11, 32, and 33 per 100,000, respectively, in 2022. Of the other heart diseases, rheumatic heart disease was the only category for which age-adjusted mortality decreased (13 to 2 per 100,000, 85% decrease) over time.

While causation was not assessed, the authors highlight several advancements in the prevention, diagnosis, and treatment of ischemic heart disease that occurred during the years from which the data were evaluated that may have contributed to decreasing mortality from ischemic heart disease (AMI in particular). The authors note, however, increasing prevalence of obesity, diabetes, hypertension and physical inactivity. While these are known risk factors for ischemic heart disease, the authors purport they may also play a role in the increased prevalence and mortality from other heart diseases by accelerating pathophysiological processes that lead to them. Additionally, the rising life expectancy over the decades studied along with better treatment for AMI contribute to increased survivorship burden with chronic ischemic heart conditions and a longer accumulation period for the development of other heart disease.

Study limitations included possible misclassification, miscoding, or oversimplification of diagnoses for the underlying cause of death. The authors additionally acknowledge there may be heterogeneity between demographic subgroups that remain unexamined and an incomplete assessment of the impact of the COVID-19 pandemic due to lack of data beyond 2022. Overall, however, the data suggest a reduction in ischemic heart disease mortality with a concurrent rise in mortality from other heart diseases, and evolving trends could

**Other heart diseases: heart failure, cardiomyopathy, hypertensive, valvular, rheumatic, arrhythmia, cardiac arrest/ventricular arrhythmia, and pulmonary heart disease. Submitted by Stephanie Hrisko, MD* impact future risk assessment related to cardiovascular mortality.

HEPATOLOGY

3. *Pan CW, Abboud Y, Chitnis A, et al. Alcohol-associated liver disease mortality.* JAMA Netw Open. *2025;8:e2514857*. doi:10.1001/jamanetworkopen.2025.14857

Noting that alcohol-associated liver disease (ALD) is responsible for one-quarter of cirrhosis-related deaths, an even larger percentage of liver-disease related hospitalizations and has become the leading reason for liver transplantation, along with exacerbation of these trends with the COVID-19 pandemic, the authors sought to use national mortality data to evaluate trends in ALD mortality in the US. The cross-sectional study used CDC WONDER mortality data for individuals 25 years and older from 1999-2022 focusing on underlying cause of death to identify ALD-related mortality [ICD-10 codes K70.xx-K70.1x for alcohol-associated hepatitis (AH) and K70.3x for alcohol-associated cirrhosis (AC)]. Age-adjusted mortality rates were calculated per 100,000 and stratified by sex, age group, and race/ethnicity. The age-specific rates from the study population were then applied to the standard 2000 US population distribution across 11 age categories allowing comparison of mortality trends over time. Joinpoint regression methods were used to assess for significant trends over the study period.

There were 436,814 (70.7% male) total deaths attributed to ALD. The mortality rate increased from 6.71 (per 100,000; 95% CI, 6.59-6.83) in 1999 to 12.53 (95%CI 12.38-12.67) in 2022, which represented an average annual percentage change (AAPC) of 3.11% (95%CI 2.07%-4.16%, P=0.001). Joinpoint regression analyses revealed three significant trends in mortality rates with relative stability from 1999-2006 (APC -0.66%), an increase from 2006-2018 (APC 3.46%) and a more rapid increase from 2018-2022 (APC 9.84%). Stratified by sex, men experienced an initial decrease in mortality 1999-2005 (APC −1.74%); whereas women experienced relative stability 1999-2006 (APC 0.34%). Both increased from 2005 (2006 for women) to 2018 (APC 2.72% men, 4.75% women) and more rapidly 2018-2022 (APC 8.45% men, 10.14% women); however, the acceleration was more pronounced for women compared to men. From 2018 to 2022 was also a period of accelerated mortality for those ages 25-44 (APC 17.69%) and the Hispanic population (APC 6.45%); whereas the American Indian/Alaska Native (AI/AN), White, and Black/African American populations experienced more pronounced accelerations in mortality from 2019-2022 (APCs 31.70%, 23.29%, and 21.45%, respectively). Absolute ALD mortality (overall, AH, and AC) stratified by demographic factors was highest for males, those 45-64, and the American Indian/Alaska Native population.

AH mortality rates increased from 0.47 to 0.76 deaths per 100,000 from 1999 to 2022 (AAPC 2.08%; 95% CI 1.27%-3.05%; P=0.001) and demonstrated only two changes in trends with initial decrease 1999-2005 (APC -5.04%) and increase 2005-2022 (APC 4.73%). The mortality for men followed these same overall trends; whereas females had an initial increase from 1999-2001 (APC 13.59%), decrease from 2001-2004 (APC -13.38%) followed by an increase from 2004-2022 (APC 6.09%). Stratified by age, there were initial decreases in AH mortality through 2005 (2007 for those 25-44) followed by increases in all age groups with the highest rate of increase in those 25-44 (2007-2022 APC 8.42%). There were varying patterns of change when stratified by race/ethnicity; however, the AI/AN population had the highest absolute mortality rate throughout and an APC of 8.43% (95% CI, 6.53-11.23, P<0.05) from 2005-2022.

AC mortality increased over time-initially from 1999-2011 (APC 1.55) and more rapidly from 2011-2022 (APC 6.75) for an absolute change from 4.09 in 1999 to 9.52 in 2022 (AAPC 4.00%; 95% CI, 3.63-4.40%; P=0.001). This trend was the same for both sexes although females experience more rapid acceleration than males (APC 2.60% vs 1.14% 1999-2011 and 8.32% vs 6.02% 2011-2022). Those in the oldest three age groups followed similar trends although the year of change in accelerated mortality was different (2009 for 45-64, 2010 for 65-84, 2012 for 85+). Those 25-44 demonstrated a different pattern with an initial overall stability (APC -0.88%), increase 2010-2018 (APC 7.07%), and strikingly more accelerated increase 2018-2022 (APC 19.51%). By race/ethnicity, AI/AN had the highest mortality rates and highest rate of acceleration from 2018-2022 (APC 18.24%); however, the Hispanic/Latino and White populations also experience increased mortality rates during those years (APC 6.84% and 9.51%, respectively).

Although the authors recognized limitations (eg, possible underreporting/underestimation due to coding/diagnostic errors or misattributed cause of death, comorbidities unaccounted for that could contribute to liver-related mortality, and limited socioeconomic data), the overall trends suggest that ALD mortality has increased over time with a narrowing sex gap, a concerning trend of accelerated mortality in the youngest age group, and accelerated mortality during the COVID 19 pandemic. There are also racial/ethnic disparities with the AI/AN population having the highest mortality rates; however, all race/ethnic groups experienced accelerated ALD mortality starting in 2018 or 2019. Future studies incorporating individual-level data on alcohol consumption, comorbidities, and sociodemographic variables may further elucidate factors contributing to these trends, particularly if they persist post-pandemic. *Submitted by Stephanie Hrisko, MD*

ONCOLOGY

4. *Sugumar K, Lie JJ, Stucky CC, et al. Pathologic Complete Response and Survival in Rectal Cancer: A Systematic Review and Meta-Analysis.* JAMA Netw Open. *2025;8:e2521197*. doi:10.1001/jamanetworkopen.2025.21197. *PMID: 40668580; PMCID: PMC12268488.*

Clinical researchers and drug trial investigators face the same difficulty that those of us interested in survival research face: the most reliable and unambiguous outcome, mortality, takes a long time to accumulate. Even when investigating drugs for a deadly cancer, this fact creates incentives to use endpoints that are surrogates for mortality, such as treatment response. In gastrointestinal cancer research, it has become commonplace to use pathologic complete response (pCR) as a surrogate endpoint. This is defined as the absence of viable tumor cells in the resected specimen after neoadjuvant chemotherapy. In this study, investigators undertook a meta-analysis to determine if there is good evidence that pCR is a reasonable surrogate marker for survival.

In all, 25 studies were determined to meet criteria for inclusion - they included both an assessment of pCR and overall survival, were in English, and involved the correct patient population (rectal cancer patients receiving neoadjuvant chemotherapy).

Meta-analysis methods are complex and involve ascertainments of bias, heterogeneity, and other metrics. The bottom line, though, is that researchers were unable to demonstrate a relationship between pCR and overall survival or disease-free survival in trials of patients undergoing neoadjuvant therapy for rectal cancer. Note that the researchers point out other studies of patient-level (rather than trial-level) data that reach the opposite conclusion. There is apparently a large debate about the appropriateness of surrogate markers in this kind of research, and this current study is more fodder for it. There are good reasons to consider that pCR may not be a good marker for survival and this could lead to ineffective therapies being approved or effective therapies being overlooked.

In my opinion, survival is the best and most reliable determinant of successful treatment for diseases like this. We should avoid the classic phenomenon of "the treatment was a success but the patient died," and perhaps also avoid the converse "the treatment failed but the patient lived." *Submitted by Steven J. Rigatti, MD, Founder, Rigatti Risk Analytics, LLC*

5. *Lian Y, Voruganti T, Lu J, Long Q, Mamtani R. Survival Trends in Urothelial Cancer Before and After ICIs and Antibody Drug Conjugates.* JAMA Netw Open. 2025;8:e2519524. doi:10.1001/jamanetworkopen.2025.19524. *PMID: 40632539; PMCID: PMC12242697.*

Metastatic urothelial cancer (MUC) typically carries a dismal prognosis, with a 95% 5-year mortality rate. However, in recent years, due to the advent of immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors, antibody-drug conjugates (ADCs) and other forms of "targeted" therapy, other poor-prognosis malignancies such as malignant melanoma have seen improved survival rates. The authors of this study sought to investigate if the approval of these new drugs has impacted the survival prospects for MUC.

Investigators utilized an electronic records system deployed nationwide in the US and excluded those who were not treated and those involved in clinical trials. Though they did not determine if patients received specific drugs, they divided the population into 3 time periods determined by the availability of them: "before ICI", "after ICI before ADC", and "after ADC". At this point some rather opaque methods were used to balance the classes - termed inverse probability of treatment weighting. Then, Kaplan-Meier plots were generated and 95% confidence intervals determined using bootstrap resampling.

Results showed that, indeed, over time the 3-year overall survival for MUC did improve, going from 19.2% to 23.3% to 27.6% in the 3 sequential time periods. While this is good news, it is not clear that the credit for this can be given to the new treatments since a determination of who received these drugs was lacking, but it certainly does fit with the overall improved survival associated with these drug classes in other malignancies. *Submitted by Steven J. Rigatti, MD, Founder, Rigatti Risk Analytics, LLC*

6. *Scilipoti P, Bratt O, Garmo H, et al. Long-Term Outcomes After Guideline-Recommended Treatment of Men with Prostate Cancer.* J Natl Compr Canc Netw. *2025;23(7):e257022.*

Nonmetastatic prostate cancer can have a very long disease trajectory, and the risk of death varies depending on both the risk category at the time of diagnosis and a patient's life expectancy. Therefore, treatment regimens can vary anywhere from active surveillance to local and systemic treatments. This recent study published by the *JNCCN* on the long-term outcomes of prostate cancer, assesses the risk of death from prostate cancer vs the risk of death from other causes. While there have been numerous prior studies on this topic, the authors point out that there is a currently gap in this literature as there are no large population-based studies on long term outcomes for men with nonmetastatic prostate cancer who are under treatment protocols specifically according to the current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines.

This study's objective was to estimate the risk of death from prostate cancer vs other causes up to 30 years after initiation of treatment for those under the NCCN Guidelines, stratified by risk category and life expectancy. Using a Swedish prostate cancer registry, which gives detailed data on workup, staging and treatment, the authors identified 63,000 men diagnosed between 2000 and 2020, median age 67 and median life expectancy 18. All had a defined disease risk category and received treatment per current NCCN guidelines with 42% receiving radical prostatectomy, 22% radiotherapy, and 20% active surveillance. Of note, 15,531 men had low-risk disease and 71% underwent active surveillance. Outcomes were simply death from prostate cancer or death from other causes at 15 and 30 years according to risk category and life expectancy.

Results of this study show that for low-risk cancer, the risk of dying from prostate cancer was about 7 times less than that of other causes at 15 years out, with the prostate cancer mortality only 5.5% and mortality from other causes 37%. Even for those who were considered very high risk, the risk of dying from prostate cancer was lower at 15 years, with prostate cancer mortality of 22%, whereas mortality from other competing causes was higher at 36%.

At 30 years, the simulated estimate for prostate cancer mortality for low-risk disease was 12%, much lower than the mortality from other causes of 77%. Even those with high-risk disease at 30 years out died more frequently from other causes with prostate cancer specific mortality of 20% vs 67% from other causes (and 30% vs 63% respectively for very high-risk disease).

As well, the authors assessed mortality according to life expectancy. Within each risk category, deaths from prostate cancer vs other causes vary according to life expectancy. For example, in men with a life expectancy >15 years, low-risk prostate cancer mortality was only 2.5% vs mortality from other causes, which was 20%. Whereas if life expectancy was <10 years, prostate cancer mortality for low-risk disease rose to 10% compared to 81% for other causes.

This study is pertinent to life insurance risk assessment in that it provides evidence that men with prostate cancer, in particular low-risk cancer are much more likely to experience mortality from other causes when treated according to current NCCN guidelines including active surveillance. A limitation of this study though would be that this data is only pertinent to those who have strictly followed these guidelines and protocols as it is not uncommon in life underwriting to observe non-adherence in the clinical setting or patient poor compliance in case reviews. *Submitted by Ted Gossard, MD*

PEDIATRIC MORTALITY

7. *Forrest CB, Koenigsberg L, Harvey FE, et al. Trends in U.S. Children's Mortality, Chronic Conditions and Obesity, Functional Status and Symptoms.* JAMA Netw Open. *Published Online: 2025;334;(6):509-516.* doi:10.1001/jama.2025.9855

In this 2025 study on US children's health, the authors preface the fact that there have been many recent important studies and reports raising concern that child health in the United States may be declining. Prior studies, however, have been limited by utilizing only single data sources or focusing on small sets of specific disease states, one health condition at a time. Therefore, in this study conducted by a team of researchers from Children's Hospital of Philadelphia (CHOP), the authors set out to determine if US children's health has changed temporally by utilizing a comprehensive set of multiple health indicators to assess and determine changes over the past 17 years.

This study design uses multiple data collection methods including the assessment of mortality statistics from the United States and 18 comparator high-income nations (referred to as OECD18), data from 5 national surveys and electronic health records from 10 pediatric health systems (PEDSnet) representing over 2 million children. One hundred and seventy-two health indicators were selected for assessment and analyzed including child mortality, chronic physical, developmental and mental health conditions, obesity, sleep health, early puberty, activity limitations, physical and emotional symptoms. The study only included individuals younger than 20 years old from 2007 to 2023.

Study results during this time period revealed that the death rate for US infants (<1 year old) was 1.78 times higher compared with the OECD18 countries (95% CI, 1.78-1.79). Similarly, the results indicate children 1-19 years old in the U.S. are 1.80 times more likely to die compared to the OECD18 (95%CI, 1.80-1.80). Prematurity and sudden infant death accounted for the largest disparity for causes of death in the infant population (RR 2.2 and 2.4, respectively). The causes of death for those in the 1-19 year old group representing the largest disparities compared to the OECD18 were firearms-related incidents (RR15.3), substance use (RR 5.3), homicide (5.3) and motor vehicle crashes (RR 2.45). Rates for suicides and cancers were similar in the United States compared to the OECD18.

Other notable findings include that a child with a chronic condition was 15%-20% more likely in 2023 compared to 2011, with annual prevalence rates rising from 39.9% to 45.7% within the PEDSnet cohort (97 chronic conditions assessed) and from 25.8% to 31.0% within the general population (15 conditions assessed). In particular, childhood obesity increased from 17% to 21%, and early onset of menses rose by over 60%. Other conditions showing the largest increases include depression (RR 3.3), sleep apnea (RR 3.2), eating disorders (RR 2.6), anxiety (RR 3.0), autism spectrum disorder, obesity, lipid metabolism and developmental disorders (risk ratios 2.1 to 2.6, respectively). As well, annual rates of 27 physical symptoms were assessed (such as abdominal pain, fatigue, cough) and 22 of these 27 symptoms increased significantly—the 3 most common being dermatologic, pain, and menstrual disorders (RR 4.8, 3.7 and 3.0, respectively).

The importance of this study lies in providing evidence-based results of observational findings that many pediatricians and family physicians, educators and parents have been making in recent years regarding the overall health of US children. As well in the life underwriting of pediatric cases, anecdotally it seems increasingly common to encounter many of the symptoms and diagnoses noted in this study, particularly mental health conditions, and along with it the challenges of accurate long-term risk assessments in this population. Being aware of and understanding these trends has obvious morbidity and mortality implications as pediatric health can have significant carry-over into adult health and subsequent long-term morbidity and mortality outcomes. *Submitted by Ted Gossard, MD*