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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 Michael L. Moore, MD, Associate Editor, Literature Review at Moorem1@Nationwide.com. We will acknowledge all contributors in each issue's installment.

CARDIOLOGY

1. Shaw LJ, Giambrone AE, Blaha MJ, et al. Long-term prognosis after coronary artery calcification testing in asymptomatic patients: A cohort study. Ann Intern Med. *2015;163:14.*

More than half of all first coronary heart disease events present as sudden death or acute myocardial infarction in a previously asymptomatic individual. For this reason, attempts are often made to identify high-risk people. Coronary artery calcium (CAC) scoring is one such means to do so, and this testing is frequently encountered in the medical records. The literature has consistently demonstrated a strong association between increasing coronary calcium burden and adverse cardiac outcomes, but it has generally been focused on shorter time intervals in the range of 5 years. In this single center observational study, 9718 consecutive asymptomatic patients without known coronary artery disease (CAD) at baseline in the Nashville, TN area underwent CAC scoring from 1996 through 1999. The subjects varied in age from 30 to 85 years, with a majority between 40 and 59 years of age. About 40% were smokers, 70% had a family history of CAD, 63% had dyslipidemia, 43% had hypertension, and 8% were diabetic. The mean follow-up duration was 14.6 years. Unadjusted all-cause mortality increased steadily with progressively higher CAC scores, ranging from 3% in subjects with scores of 0, and 6% in subjects with scores of 1-10, to 28% in subjects having scores over 1000. Similarly, corresponding hazard ratios increased from 1.68 for scores of 1-10 to 6.26 for scores of 1000 or greater. After adjusting for CAD risk factors, CAC score remained highly predictive of time to all-cause mortality. Subjects were divided into quartiles according to their predicted risk of 15-year mortality, and increasing CAC scores were associated with higher risk for death with each of those groups. Adding the CAC score, with cut points ranging from less than 7.5% to over 22.5% mortality, to a model with CAD risk factors led to a categorical net reclassification improvement of 0.21, a magnitude felt to be substantial by the researchers. Compared with the model using risk factors alone, the model with the CAC added correctly reclassified almost 28% of patients who died during follow-up, but incorrectly reclassified about 7% of survivors to a higher-risk category. A total of 936 subjects died during the study period. Of these, 3% had no detectable CAC. For the remainder, an increasing percentage of each higher CAC score category died. Nearly half (49%) of those who died had CAC scores of 400-999 (21%) or over 1000 (28%), whereas the per-

centage diminished with each lower CAC category (101-399 – 14%, 11-100 – 9%, and 1-10 – 6%). The key takeaway from this research is that CAC scores have persisting predictive value and can accurately predict 15-year all-cause mortality in asymptomatic individuals. The authors noted that use of data from a single center, and measurement of CAC only one time, might somewhat limit study conclusions. *Submitted by David S. Williams, MD*

GASTROENTEROLOGY

2. Kroep S, Lansdorp-Vogelaar I, Rubenstein JH, et al. An accurate cancer incidence in Barrett's esophagus: A best estimate using published data and modeling. Gastroenterology. *2015;149:577-585.*

I found this study interesting because it better clarified the risk of an impairment I see almost every day. These investigators attempted to reconcile differences in Barrett's esophagus to esophageal adenocarcinoma progression rates reported in the literature. Because the true risk of progression is uncertain, they used the ERASMUS/UW esophageal adenocarcinoma model to more accurately estimate cancer incidence in Barrett's esophagus. This model was previously developed by researchers at Erasmus Medical Center University in the Netherlands and the University of Washington in the United States. Simulation modeling was employed to alternately reflect surveillance conditions of population-based vs prospective studies. They adjusted the model to reproduce the design of population-based studies with realistic inaccuracies in surveillance and diagnoses, then calibrated the model to match the annual progression rates (0.18%) reported by population-based studies. They then used the model to simulate the population based on 3 scenarios:

1. Without surveillance
2. With a population-based study design in which 38% of patients with Barrett's esophagus and no dysplasia and 52% of patients with low-grade dysplasia received initial surveillance
3. With a prospective design in which 100% of patients received initial surveillance.

Finally, they predicted progression rates for population-based and prospective study designs and for different follow-up periods and compared them with published data. The modeled cohort had a mean age of 65 years at the time of Barrett's esophagus diagnosis, and subjects were included until cancer developed, death occurred, or follow-up ended. In the first 5 years of follow-up, the mean annual rate of progression from Barrett's esophagus to esophageal adenocarcinoma was 0.19%, very similar to recent population-based study findings. When the model was calibrated to characteristics of prospective cohort studies, it predicted a progression rate of 0.36% annually, similar to the published rate of 0.41% per year. After 20 years, the estimated annual progression rates for these 2 respective scenarios increased to 0.63% and 0.65%, with cumulative incidences of esophageal adenocarcinoma of 9.1% and 9.5%. The relative differences between the progression rates of both study designs decreased from 91% after 5 years to 5% after 20 years. The difference between the lower progression rates found in the population-based studies and the higher rates found in prospective studies was thought to be due to detection bias from endoscopic surveillance. The short-term risk for the progression to adenocarcinoma is probably closer to the population-based study estimates because less surveillance was performed in those studies. One limitation of these results is that they apply to older populations age 65 and up. *Submitted by David S. Williams, MD*

GERIATRICS

3. *McIsaac DI, Bryson GL, van Walraven C. Association of Frailty and 1-Year Postoperative Mortality Following Major elective*

Noncardiac Surgery McIsaac DI. JAMA Surgery. *2016;151(6):538-545.*

Frailty is well-understood to be associated with mortality in general and post-operative mortality in particular. The authors of this study out of Ontario sought to establish the pattern of post-operative mortality in those with frailty-defining conditions compared to those without such conditions. They used databases available through Canada's public health system to find 202,811 patients who had undergone major elective surgery after age 65. Specific major surgeries included total hip and knee arthroplasty, carotid endarterectomy, nephrectomy, cystectomy, liver resection, large bowel resection, nephrectomy and pancreaticoduodenectomy.

Frailty was determined using a proprietary instrument devised by Johns Hopkins which examines 12 clusters of diagnoses to arrive at a binary (yes/no) indicator of frailty. Baseline characteristics showed that the frail group was significantly older and had more comorbidities than the non-frail group. Using Cox models were used to generate hazard ratios and display the estimated hazard functions by post-operative day stratified by frailty status. This showed that the highest impact of frailty on mortality occurred in the first few post-operative days. After that the hazard ratios rapidly declined but did not approach 1 – settling in at around 2.3 for the entire cohort.

The frail/non-frail hazard ratio was highest for the joint replacement surgeries and lowest for liver resection and Whipple procedures. This is both interesting and reasonable – as the joint procedure may often be done on fairly healthy individuals, magnifying the difference between them and their frail counterparts. Whereas a Whipple procedure, and the reasons one must have a Whipple procedure, are so laden with mortality risk that frailty hardly matters.

The bottom line for the life insurance medical director is that frailty is significantly associated with mortality risk which is magnified by major surgery, and that risk persists for at least one year. *Submitted by Steven J. Rigatti, MD*

INFECTIOUS DISEASE

4. Roberts E, Wessely S, Chalder T, Chang CK, Hotopf M. Mortality of people with chronic fatigue syndrome: a retrospective study cohort study in England and Wales. Lancet. *2016;387:1638-1648.*

This was a retrospective study of 2147 individuals in Great Britain who had been diagnosed with chronic fatigue syndrome from 2007 through 2013. Of the participants, 1533 were women of whom 11 died, and 614 were men of whom 6 died. Comparison was made to the general population to see if these rates of death were higher for both all cause and cancer specific mortality. It was found that the standardized mortality rate was not significantly different for either of these 2 areas. However, there was a significant difference in the rate of suicide. Specifically, the standardized mortality rate was nearly 7 times that of the general population.

Looking at the data even closer, it is interesting that the median age of all participants with chronic fatigue was 39.1 years old; whereas with those patients who died, the median age was 48.3 years. The other striking statistic is that the suicide mortality rate for women had a standardized mortality rate of 9.49 and the Caucasian population had a mortality rate of 9.12. It was also noted that the population with a lifetime depression diagnosis had a mortality ratio of 3.06, which is what one might expect. However, those *without* the lifetime depression diagnosis had a slightly higher mortality ratio of 4.57.

What can we learn from this study? First the reassuring news is that there is not a higher than expected rate of overall mortality nor cancer related mortality in this relatively small study. It is alarming, however, that the suicide rate is substantially higher than expected with 2 distinct groups at higher risk. Those being: women and Caucasians. Sur-

prisingly, the mortality ratio from suicide was higher in those without a lifetime diagnosis of depression compared to those who carried that diagnosis. I think the point to carry away from the study is that when faced with a history of chronic fatigue syndrome for mortality risk assessment, the medical director is well advised to watch for signs that could signal a risk for suicide particularly in the female and Caucasian cohort. *Submitted by Michael L Moore, MD*

5. Prescott, HC, Prescott HC, Osterholzer JJ, Langa KM, Angus DC, Iwashyna TJ. Late mortality after sepsis: propensity match cohort study. BMJ. *2016;353:i2375.*

This study, out of the University of Michigan, demonstrates a how careful study design and matching can be used to address a thorny clinical debate using data. Several prior studies had shown that patients leaving the hospital after a diagnosis of sepsis experience higher levels of mortality compared to the community population. However, there had been significant debate over whether this was a direct effect of sepsis or a manifestation of the higher burden of comorbidities among those who were hospitalized for sepsis.

The authors used the Health and Retirement Study, a cohort of 37,000 individuals over age 50. This cohort is linked to Medicare claims data and is probability-sampled to be demographically representative of the US population. Researchers selected those who were age 65 or older at some point during the study period of 1998 to 2008. The primary study group consisted of those admitted to hospital with sepsis. Three different control groups were then constructed: 1) Those admitted to hospital with a non-septic infection, 2) Those admitted to hospital with "sterile inflammation" (inflammation without infection, such as trauma, burns or pancreatitis), and 3) Those not admitted to the hospital. For each control group, matching was carried out based on age, sex and a propensity score – that is a risk score designed to predict the risk of sepsis in two years. Not all of the study subjects could be successfully matched to members of the other cohorts, and these were dropped from analysis for that particular comparison. The outcome was mortality between 31 days and 2 years post discharge, and was measured by odds ratio (OR). The authors also reported the OR for smaller time periods, 31 to 90 days, 91 to 180 days, 181 days to 1 year and >1 to 2 years.

The results showed fairly strong evidence that there is a substantial increase in the odds of mortality after an admission for sepsis. This increase, in relative terms, is highest in the early days after admission and tapers off in year 2. This elevation is present compared to the non-hospitalized cohort, as well as both hospitalized groups. For the sepsis group vs the non-hospitalized group, the odds ratios for mortality for the 31-90 day, 91-180 day, 181 day to 1 year, and >1 to 2-year time periods were 9.8, 4.0, 3.2 and 1.6, respectively. For the sepsis group vs the non-sepsis infection group, the corresponding odds ratios were 2.5, 1.8, 1.6 and 1.0, respectively. For the sepsis group vs. the sterile inflammation group the corresponding odds ratios were 3.6, 2.0, 1.7, and 1.4, respectively.

The implications of this study to life insurance medicine are fairly significant. While it is not uncommon to see recommendations for postponement after a severe illness, the timespan of the increased risk here is higher than might be thought on clinical judgement alone. Note also that the fact that the odds ratios are quite a bit higher in the comparison to non-hospitalized individuals implies that the other causes of hospitalization (non-septic infection and sterile inflammation) also carry fairly long "tails" of mortality. *Submitted by Steven J. Rigatti, MD*

NEUROLOGY

6. Long C, Amoasii L, Mireault AA, et al. CRISPR Gene Editing Cures Muscular Dystrophy in Mice. Science. *2016;351:400-403.*

While it is unusual for us to review nonmedical journal articles it was thought

that this article which appeared in S*cience* may have such impact in treating what has thought to have been incurable diseases that it was worth bringing to the attention of the readership.

While gene editing techniques have been around for many years, the use of the CRISPR-Cas9 technique has allowed genes to be edited easily, accurately and most importantly in living hosts. This article reports that 3 independent research groups have successfully treated mice who model Duchenne muscular dystrophy. A CRISPR created complex which produces a truncated but functional dystrophin protein was introduced into the mice via an adenovirus vector which carried it to both skeletal and cardiac muscle cells. The introduction of this genetic material allowed production of enough dystrophin protein to significantly improve muscle function. Significantly, the effect of this one-time treatment seemed to improve over time.

While we are likely years away from this becoming a standardized treatment, it is exciting to see that significant progress is being made in the treatment of these dread diseases. *Submitted by Michael L Moore, MD*

7. Li L, Yiin GS1, Geraghty OC, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischemic attack and ischemic stroke: A population-based study. Lancet Neurol. *2015;14:903-914.*

About a third of transient ischemic attacks (TIAs) and strokes do not have a detectable etiology, but appear to be embolic in origin and are known as "cryptogenic" TIA or stroke. These types of stroke and TIA can undermine attempts at secondary prevention. We see such cases frequently in underwriting, particularly in younger applicants. Most previous studies of risk factors or prognosis of cryptogenic stroke and TIA have been hospital based. To better understand this phenomenon, these UK researchers examined risk factor profiles and outcomes of a large number of stroke and TIA patients in a large population-based study. They enrolled 1607 subjects with stroke and 948 subjects with TIA and followed them for as long as 10 years. Overall, 812 of the cases (32%) were classified as cryptogenic, and these subjects were significantly less likely to have atherosclerotic risk factors. Relative to large artery stroke and TIA subjects, cryptogenic stroke and TIA subjects had significantly less hypertension, diabetes, and hyperlipidemia. Compared with subjects who had small vessel disease or large artery stroke, the proportion of cryptogenic stroke patients who were dead or dependent at 6 months was similar: 23% of the cryptogenic group vs 27% of the other groups. Similar too was the 10-year risk for recurrent events: 32% of the cryptogenic group vs 27% of the other groups. Subjects with cryptogenic stroke or TIA had lower risk for early recurrent stroke than did patients with other stroke subtypes. This study confirmed that cryptogenic stroke and TIA are relatively common events. The burden of atherosclerotic risk factors tends to be much lower in these patients. The short-term prognosis for recurrent events is more benign, but rates of death and disability after cryptogenic stroke are similar to after other stroke subtypes. Those having had cryptogenic events had a lower frequency of co-morbid atherosclerotic disease, and a lower risk of acute coronary events compared with patients with events of known cause. Likewise, patients with cryptogenic events had lower long-term risk of new atrial fibrillation, and no excess prevalence of paroxysmal atrial fibrillation or minor-risk cardiac abnormalities on baseline investigation. Limitations of this study included the occasional subjectivity associated with precise diagnosis of a TIA, as well as the definition of what constitutes a "complete" investigation of all possible causes of a cerebrovascular event. *Submitted by David S. Williams, MD*