This month’s feature highlights three articles, one of which focuses on COVID-19, that appear in the current issue of Mayo Clinic Proceedings. These articles are also featured on the Mayo Clinic Proceedings’ YouTube Channel (https://youtu.be/AM0wvyn98_o).

**COVID-19 AND INDIVIDUALIZED MEDICINE**

Individual responses to SARS-CoV-2 infection vary widely, ranging from an entirely asymptomatic state to the fulminant appearance of COVID-19 and attendant fatality. Since the pandemic began it became apparent that the risk of developing COVID-19 and the severity of the ensuing disease may be influenced by individual characteristics (age, sex, race/ethnicity, obesity) and behaviors (smoking, sedentary lifestyle), coexisting diseases (respiratory, cardiovascular, kidney diseases, and others), immune status (immunosuppression, immunosenescence), socioeconomic factors, and disparities in health care. Yet it is also recognized that individuals who seem prone to developing COVID-19 and exhibiting a progressive course may not do so, whereas others who appear relatively risk-free may contract and succumb to the disease. In the present issue of Mayo Clinic Proceedings, Pereira et al provide a comprehensive and discerning overview of the heterogeneity in the susceptibility to and severity of COVID-19, beginning with discussions of sex differences in COVID-19 and characteristics of those with severe, milder, or no disease. Notable findings as regards the latter include the fact that asymptomatic individuals or those in the presymptom phase can readily transmit the disease because of abundant viral RNA in their upper airway secretions and, as compared with symptomatic individuals, may have more protracted viral shedding and less vigorous immune responses. Differences in COVID-19-caused mortality that occur among states in the United States may reflect, in part, differences in race/ethnicity, socioeconomic factors, and health care disparities. Differences in mortality among countries may reflect, in part, genetic differences; because of such differences East Asian populations, compared with European populations, may have higher expression of ACE2 (the cell surface receptor which enables viral entry into cells). Genetic variation may influence manifestations of COVID-19 in other ways; for example, variants in the ACE2 gene may diminish the efficacy of ACE2 in serving as a receptor for viral cell entry; and certain single nucleotide polymorphisms may influence the TMPRSS2 gene expression and its protease activity in priming the spike protein of SARS-CoV-2. Such priming is a necessary first step before SARS-CoV-2 engages the ACE2 receptor. Disease outcomes may also be influenced by specific ABO groups, HLA antigens, and ancestral haplotypes. The propensity for greater severity of COVID-19 in males as compared with females provides a salient example of the involvement of multiple mechanisms: males exhibit higher ACE2 levels which possibly reflect the fact that the ACE2 gene resides on the X chromosome; males lack the anti-inflammatory and cytoprotective effects of estrogens; and male sex hormones are potent inducers of the TMPRSS2 gene. Additionally, females exhibit higher expression of TLR7, a receptor that recognizes viral RNA after which
increased production of interferon ensues; interferon constitutes a major early defense against viral infection. Disease outcomes are determined not only by characteristics of the host but also of the virus itself; for example, the D614G variant of the spike protein of SARS-CoV-2 promotes viral transmission. After these in-depth discussions, Pereira et al then delineate how understanding the heterogeneity of COVID-19 may advance clinical management in at least three ways. First, understanding the clinical and biochemical determinants of the severity of COVID-19 can lead to the development of risk prediction models which may aid in assessing which patients may be prioritized for vaccination, may require hospitalization and/or admission to the intensive care unit, respond to specific therapies, and be appropriately recruited for clinical trials (that is, providing the right drug to the right patient such that responses to a given drug and outcomes can be meaningfully evaluated). Second, heterogeneity of responses also pertains to COVID-19 antibody testing in that patients with severe disease develop higher levels of antibodies whereas patients with milder disease become seronegative sooner in the recovery phase or never exhibit seroconversion. Vaccine development is the third clinical area influenced by disease heterogeneity. Immune responses to SARS-CoV-2 include activation and proliferation of B and T cell subsets, and elucidating which particular subsets foil the disease are relevant to the development of vaccines (as well as novel therapies). There is considerable variation in immune responses and this challenges vaccine development because of less immune responsitivity in some individuals (and thus less benefit from vaccination) and the possibility of disease enhancement in others. In concluding their review, Pereira et al emphasize the need to incorporate in the electronic health record predictive tools that call attention to the high risk patient; the potential of artificial intelligence, digital platforms, and sensor technology in meeting the challenges arising from heterogeneity of COVID-19; and the need for studies of genetic factors that underlie disease heterogeneity. Pereira et al are to be commended for providing this masterful and timely analysis of a critical and challenging aspect of COVID-19.


ADVERSE EFFECTS OF INACTIVITY AND LOW FITNESS ON POPULATION HEALTH

Abundant literature supports the view that low cardiorespiratory fitness (CRF) and physical inactivity significantly increase mortality from cardiovascular and other diseases. This has led to the guideline that individuals should engage in at least 150 minutes per week of moderate intensity aerobic activity, a recommendation followed by only a minority of the US population. In the present issue of Mayo Clinic Proceedings, Myers et al address the adverse impact of physical inactivity and low CRF on mortality in a population of 5890 male subjects who, between 1992 and 2014, underwent clinical evaluation by maximal exercise testing. Low CRF was defined as less than 5 METs and physical inactivity was defined as less than 150 minutes of moderate physical activity per week. To evaluate outcomes at a population level, the authors determine the population-attributable risk (PAR) and exposure impact number (EIN). As specifically applied to this study and as stated by the authors the PAR is “the number of deaths that would not occur if physical inactivity or low fitness were removed as risk factors,” while the EIN is “the number of subjects removed from the low CRF or inactive categories necessary to eliminate 1 death.” These indices reflect the fact that the higher the PAR the greater the adverse effect of the risk factor, while the lower the EIN the greater the adverse effect of the risk factor. The data in this study demonstrate that a low CRF was associated with substantial increases in mortality, and mortality decreased as higher METs were achieved. Mortality was also increased in those with low physical activity, with a 2-fold higher
risk in the least active as compared with the most active individuals. Remarkably, PAR was highest in individuals with low CRF when compared with other risk factors such as hypertension, physical inactivity, smoking, and diabetes; EIN was the lowest in individuals with low CRF when compared with diabetes, smoking, hypertension, and physical activity; the PAR for low CRF tripled that for diabetes; and the EIN for low CRF was one-fifth of that exhibited for hypertension. These findings are important from the standpoint of individual patient care as they emphasize the need for enhanced physical activity and CRF in improving health and decreasing mortality. As highlighted by the authors, these findings are especially important from the perspective of public health policy: some 50 billion dollars are spent annually in the management of hypertension in the United States (and vastly more on the management of diabetes). Health care counseling and policies designed to improve physical activity and CRF will substantively improve the health of individuals and the population at large, all of which may be achieved at only a fraction of costs entailed in the management of diabetes and hypertension.


FEMALE SEX, AGE, AND ACUTE MYOCARDIAL INFARCTION

As is true for so many diseases, the incidence and outcomes of acute myocardial infarction (AMI) exhibit sex-based and age-related differences. However, whether age per se may modulate these sex-related outcomes for this disease has been examined by very few, if any, studies involving large numbers of patients. In the present issue of Mayo Clinic Proceedings, Alkhouri et al used the National Inpatient Sample to identify more than 6,700,000 hospitalizations for AMI between 2003 and 2015. Analyses of the incidence, management, and outcomes of AMI (both STEMI and NSTEMI) in men and women were undertaken in 4 age ranges, namely, <45, 45 to 64, 65 to 84, and ≥85 years of age. The major findings of Alkhouri et al were that across all age ranges women as compared with men exhibited a lower incidence of AMI; were less likely to undergo coronary angiography, percutaneous coronary intervention, or coronary artery bypass grafting for NSTEMI and to undergo coronary angiography or percutaneous coronary intervention for STEMI; and for either subtype of AMI, were less likely to receive mechanical circulatory support. Notably, women as compared with men exhibited a higher mortality and a higher incidence of major post-MI complications in the young and middle age range; in the older age ranges, women exhibited generally better outcomes than men. The finding that women receive less invasive management as compared with men has been observed previously in the literature, and possible explanations, as discussed by Alkhouri et al, may include the fact that AMI presentations may be different or delayed in women; there may be greater acceptance for more conservative care; and invasive management for whatever reason may be less efficacious in women. The strengths of this study by Alkhouri et al are many including the size of population analyzed, the rigor of the analysis, its under-scoring of the sex-based disparity in interventional management of AMI, and that age is a critical modulator of sex-related differences as evidenced by the higher mortality and worse outcomes which occur in young and middle age women.


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