# Chapter 7
# Health Disparities in ARDS

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## Key Points

- Compared to other respiratory diseases, health disparities related to acute lung injury and acute respiratory distress syndrome outcomes have only recently been recognized and investigated.
- African Americans appear to be at increased risk of mortality due to acute lung injury.

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- Genetic variation may contribute to variability in acute lung injury outcomes by race and ethnicity, and several risk SNPs have been identified.
- Beyond genetic variation, other potential contributors to health disparities in acute lung injury outcomes include differences in risk related to factors that predispose to acute lung injury including sepsis, differences in the prevalence and severity of comorbid illness, and differences in health care quality and access to care.

## Overview: Health Disparities and ARDS

In the context of health, the term "disparity" signifies not only a difference in health quality and access to care among groups, but it also denotes inequality and/or unfairness. Thus, "disparity" is inherently controversial and difficult to quantify. Multiple definitions of health disparities exist, and a variety of methods have been employed to measure these disparities. The National Healthcare Disparities Reports (NHDR) defines health disparity as "all differences among populations in measures of health and health care" and therefore assesses differences in group means. However, a limitation of this definition is that it does not account for health status and age differences between populations. The Institute of Medicine (IOM) defines health care disparities in the Unequal Treatment Report as "differences in health care services received by the two groups that are not due to differences in the underlying health care needs or preferences of the members groups." Under this definition, various factors are assessed in addition to differences in health status, such as differences due to the operation of health care systems, the legal and regulatory climate, and discrimination [1]. Health disparities are present when differences in health outcomes adversely affect groups of people who have experienced greater obstacles to health on the basis of factors including race, ethnicity, gender, age, and/or geographic location, such as rural and border areas. The adverse impact of health disparities extends to a much broader, societal level due to the resulting economic consequences, including the rising cost of health care and lost work-related efficiency and productivity.

Minority populations, including Hispanics and African Americans, are more frequently affected by these inequities, and these populations experience greater mortality from common complex health disorders than non-Hispanic whites. In general, minorities receive less and poorer quality health care. The combined direct and indirect cost of health disparities for minorities in the USA between 2003 and 2006 was estimated at $1.23 trillion; direct medical expenditures were estimated at $230 billion and indirect costs associated with illness and premature death were approximately $1 trillion [2]. Eliminating health inequalities for minorities would greatly reduce indirect costs on society, impacting worker productivity and losses from premature death. The U.S. Department of Health and Human Services has acknowledged the importance of addressing social determinants of health through the Healthy People program, which provides science-based 10-year objectives for improving the health of Americans; a major goal outlined for 2020 is to eliminate disparities and improve the health of all groups (www.healthypeople.gov).

Because racial and ethnic identity are not only related to genetic ancestry but are also inextricably linked to socioeconomic status, cultural/historical heritage, and access to health care, the study of health disparities in racial/ethnic minority groups poses many challenges, and this is particularly true for health disparities research related to critical illness. In comparison to other respiratory diseases, health disparities in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have only recently begun to be described and investigated. In the USA, racial/ethnic minorities suffer disproportionately from preventable and treatable conditions including ALI and ARDS among the critically ill [3, 4]. ARDS is a heterogeneous critical illness with mortality often exceeding 30–40 % [5, 6]. ARDS is characterized by acute diffuse inflammatory lung injury, increased vascular permeability, and flooding of alveoli with protein-rich fluid, resulting in devastating physiologic derangements that cause acute respiratory failure. Under the Berlin definition, ALI and ARDS are defined by acute onset bilateral infiltrates on chest imaging associated with hypoxemia determined by a reduced ratio of arterial partial pressure of oxygen ($PaO_2$) to fraction of inspired oxygen ($FiO_2$) in the absence of left atrial hypertension. ARDS severity is based on the degree of hypoxemia: mild ($PaO_2/FiO_2$ 200–300), moderate ($PaO_2/FiO_2$ 100–200), and severe ($PaO_2/FiO_2 < 100$), and each category has a mortality index. Compared with the previous AECC definition, the current Berlin definition is better at predicting mortality [7]. Recent epidemiologic studies indicate that minority populations demonstrate increased risk for ARDS and associated mortality [8–10]. This chapter will review various factors that may contribute to this important and devastating disparity.

## Health Disparities in ARDS Risk and Outcomes

Epidemiologic studies have demonstrated differences in ARDS incidence and mortality by race/ethnicity. Moss and Mannino (2002) reported that the annual ARDS mortality rates in the USA were higher for African American patients when compared with whites during 1979–1996. Further, African American men had the highest annual age-adjusted mortality rate from ARDS, compared with other race/ethnicity and gender subgroups [8]. This raised the question of whether the increased mortality among African Americans was associated with higher risk of diagnoses leading to ARDS, such as pneumonia, sepsis, or trauma; whether race/ethnicity may influence the care of these patients with ARDS; and/or whether socioeconomic status and access to care may contribute to these outcomes. A recent multicenter observational cohort study of 5201 patients at risk for ALI showed no significant difference in in-hospital ALI-related mortality by race or sex after adjusting for potential confounders [11]. However, it demonstrated differences in clinical presentation based on race; African Americans more frequently presented with ARDS in the setting of pneumonia, sepsis, or shock and had higher severity of illness [11]. While African Americans were more likely to present with greater severity of illness in this study, they were overall less likely to develop ALI compared to white patients (4.5 % vs. 6.5 %, $p = 0.014$). This study's findings are in contrast to prior

work published by investigators from the ARDS Network which reported that African American and Hispanic patients are at significantly higher risk of death from ARDS compared to white patients [9]. In summary, the limited available evidence suggests that African Americans are at higher risk of ARDS-related mortality but may be at lower risk of developing ARDS, and likewise Hispanics appear to be at higher risk of death due to ARDS.

## *Factors Influencing Health Disparities in ARDS*

Differences in the quality and intensity of care by race may influence racial differences in ARDS-related outcomes. For example, differences also exist in the intensity of ICU care at the end of life in non-white patients compared with white patients [12]. Similarly in one study black patients with pneumonia were less likely to receive antibiotics within the recommended 4-h window than white patients, even after adjusting for severity of illness and other patient factors [13]. Hospital characteristics are other contributors that may be correlated to outcome disparities. For instance, minorities with severe sepsis are more likely to be treated in larger urban academic centers, and differences in care variation across hospitals have been demonstrated [14, 15].

As noted throughout this book, racial and ethnic minorities experience higher levels of poverty. Income is linked with health regardless of racial or ethnic group, but differences in health status by income do not completely capture the differences by race or ethnicity [16]. Minorities of low SES are more susceptible to experiencing diminished quality of life and increased burden of respiratory disease, as they are up to 14 times more likely to have respiratory diseases as compared to higher SES social groups [17]. Likewise environmental exposure and occupational hazards are more common among the lowest socioeconomic groups as well, with the lungs being the most immediate organ affected by environmental exposures such as tobacco smoke, air pollution, and occupational inhalants. Multidisciplinary strategies such as reducing environmental exposures, promoting a healthy life style, and improving the quality of health care are likely needed to significantly ameliorate these disparities. However, the role that these individual factors play in the development of ARDS remains largely unexplored, cultural competence at all levels of care has been recommended as a strategy to address disparities, based on the premise that improving provider-patient communication is an important component of addressing differences in quality of care that are based on the race, ethnicity, or culture of the patient [18]. Cultural competence enables providers to deliver services that are respectful of and responsive to the health beliefs, practices, and cultural and linguistic needs of diverse patients and favors treatment adherence. A cross-sectional analysis of the multi-center, randomized trials conducted by the ARDS Network from 1996 to 2005 failed to find significant evidence of sex or racial/ethnic minorities underrepresentation in ARDS clinical trials [19, 20], although it should be noted that this study also reported that Black, Hispanic, and American/Indian/Alaskan Native patients were more often

**Table 7.1** Most common conditions associated with ARDS by race

| Race | Condition | Reference |
|---|---|---|
| African Americans | Sepsis, pneumonia | [11, 14, 24] |
| Asians | Aspiration, trauma | [10, 11] |
| Hispanics | Sepsis, trauma | [9, 11] |
| Whites | Surgery | [9, 11] |

unable to be consented for research participation due to the lack of surrogate or family refusal. This may reflect existing mistrust of the research environment, lack of research staff diversity, and/or language and communication barriers [19]. Although the majority of studies on disparities in critical care illnesses have focused primarily on race differences, Hispanic patients have not been sufficiently represented in prior studies [6].

## *Predisposing Conditions and ARDS*

While ARDS is associated with preexistent conditions such as sepsis, trauma, gastric acid aspiration, excessive mechanical ventilation and pneumonia [21–23], only a fraction of patients exposed to ARD-Sinciting events actually develop the syndrome. Epidemiologic studies over the past several decades have shown that race and gender influence sepsis-related deaths, and sepsis is a major risk factor for ARDS. Prior work has suggested that at least one possible reason for racial differences in ARDS mortality may be due to the fact that African Americans are thought to be at higher risk of severe sepsis [8]. Severe sepsis, defined by international consensus conference criteria, includes an infection plus acute organ dysfunction, and it represents a considerable public health burden that afflicts over 750,000 Americans each year. Sepsis was the most at-risk common condition associated with non-cardiogenic acute respiratory failure across racial and ethnic groups according to the National Hospital Discharge Survey (NHDS) database (1992–2007) [24]. African Americans have an increased risk for sepsis and other high-risk conditions that predispose them to develop acute respiratory failure. This increased susceptibility may be multifactorial, including higher proportion of chronic conditions over extended time and environmental, socioeconomic, and genetic factors. Table 7.1 shows the most common predisposing conditions associated with ARDS by race category [9–11, 14, 24]. African Americans have the highest rate of severe sepsis, followed by Latinos then whites; this corresponds with a rate ratio (RR) of 1.7 for blacks and 1.1 for Latinos, compared to whites [25]. Moreover, blacks had the highest sepsis-related mortality compared to other races when adjusting for age and sex, followed by Hispanics and whites ($p < 0.0001$). In complicated cases of severe sepsis requiring ICU admission, blacks with severe sepsis were more likely to die if they were admitted to the ICU ($p < 0.0001$) [14].

According to data from a National Trauma Data Bank study, there was no evidence to support significant differences in ARDS incidence, severity, or mortality based on race in trauma patients [10]. Interestingly, in a previous study, Black and

**Table 7.2** Comorbidities associated with severe sepsis

| Sepsis comorbidity | Non-Latino Black (%) | Latinos (%) | Non-Latinos White (%) |
|---|---|---|---|
| Diabetes | 18.7 | 19.7 | 15.1 |
| Renal infection | 35.3 | 30.2 | 32.7 |
| Lung infection | 38 | 38.6 | 42.6 |
| ICU admission | 54.3 | 52 | 53.6 |

*Source*: Adapted from Barnato, AE et al. [14]

Hispanic patients showed a significantly higher risk of death compared to whites, and this risk seemed to be associated with illness severity in blacks but not in Hispanics [9]. In addition, Hispanics were reported to have significantly fewer ventilator-free days compared to whites and African Americans [9]. Racial differences in predisposing comorbidities and outcomes have been documented as well. Mortality rate in ARDS is higher in African Americans and Hispanics than in other groups in the USA [8]. Likewise, the incidence of sepsis among black patients is proportionally higher compared to white patients [9, 14, 24]. The difference in the outcomes between subjects with sepsis associated with other comorbidities suggests that the presence of comorbidities may place patients at a higher mortality risk if ARDS is present (Table 7.2).

## Genetic Susceptibility as a Contributor to ARDS Disparities

Given that African Americans and Latinos have increased risk of ALI mortality, significant interest exists for the identification of genetic and non-genetic factors potentially contributing to ARDS susceptibility and prognosis [26]. Individual genetic variation may be responsible for conferring differing risks with respect to ALI outcomes among different racial groups.

In the era of personalized medicine, study of the human genome is providing increasing insight into the role of race and ethnic variations in multiple complex disorders including the influence of single nucleotide polymorphisms (SNPs) on susceptibility and severity of sepsis and sepsis-associated ARDS [27–35]. Due to the increasing number of epidemiologic studies that implicate race may play a role in the large heterogeneity associated with ARDS outcomes, several strategies have been developed to identify race-specific candidate genes. Using a candidate gene-based case-control association study, sampling distinct individuals from the population of patients and controls was performed to assess differences in the frequency of variants in genes of interest. Candidate gene variants were identified by analyzing publicly known SNPs or via gene sequencing [36] and SNPs associated with human ARDS were determined, with unique variants observed specifically in African Americans. Highly differentially regulated genes between the apex and base regions included several genes commonly associated with ARDS: vascular endothelial growth factor (VEGF), thrombospondin 1 (THBS1), plasminogen activator inhibitor 1 (PAI-1),

transforming growth factor β (TGF-β), and pre-B cell colony-enhancing factor (PBEF) [37]. Several variants of genes involved in inflammatory and innate responses to infection showed different allelic frequencies by race and gender in ARDS and sepsis, suggesting that race and gender may have variable inherent response to infection [38]. Studies, however, suggest that genetic variation alone does not fully explain the differences in outcomes with respect to common acute critical illness. Immunologic and inflammatory diseases are associated with a large number of genetic markers with a large variance among different ethnic populations. Examples of this variation have been associated with individuals of African descent and individuals of non-African descent with either the presence of diseases associated with the inflammatory and/or infection pathways, or for which the susceptibility allele occurs at a larger frequency. Examples include the 237G allele of the beta chain of the high-affinity IgE receptor [FCER1B]; the -589T allele of interleukin (IL)-4 receptor alpha; the P46L (c.224C>T) variant in the gene encoding member 1A of tumor necrosis factor receptor superfamily (TNFRSF1A); the -174G/G genotype in the pro-inflammatory cytokine IL-6 gene; and the -401A allele of RANTES [35, 39]. Moreover, there are gene variants that have been associated with sepsis development and ARDS. For example, Saleh et al. identified CGA (Arg) codon resulting in a full-length caspase polypeptide (Csp12-L) associated with severe sepsis and a higher mortality due to sepsis; this variant confers hypo-responsiveness to LPS-stimulated cytokine production and is present in approximately 20 % of African descent but is absent in Europeans and Asians [40]. Tumor necrosis factor alpha has also been associated with ARDS. Similarly, the functional rs2814778 SNP in the gene encoding Duffy antigen/receptor for chemokines is associated with worse clinical outcomes among African Americans with ARDS, possibly via an increase in circulating IL-8 [41].

Candidate gene-based studies from our laboratory utilizing preclinical models of sepsis and ARDS identified a number of genes that have been shown to be associated with features of ARDS pathobiology [28, 30, 35, 36, 42, 43]. For example, two genes associated with ARDS susceptibility include NAMPT/PBEF (*NAMPT*) and myosin light chain kinase (*MYLK*). PBEF was identified from high-throughput expression profiling in animal models of ARDS and in human patients following ALI [35, 43]. PBEF protein levels were elevated in human bronchoalveolar lavage and serum samples from patients with ARDS, and also DNA sequencing identified two SNPs in the PBEF promoter that were overrepresented in patients with sepsis-induced ARDS [26]. Variants in the promoter region of PBEF were shown to confer a 7.7-fold higher risk of sepsis-associated ALI ($p < 0.001$) compared with both individuals with severe sepsis and healthy control subjects. Additionally, functional studies have further validated PBEF as a novel biomarker in ARDS [30, 39]. PBEF is not only an essential participant in ventilator-induced lung injury (VILI), but also a key regulator of cellular apoptosis and vascular barrier regulation.

MYLK is a multifunctional $Ca^{2+}$/calmodulin (CaM)-dependent kinase in endothelium that contributes to endothelial contraction and barrier dysfunction. The human MYLK encodes three proteins including non-muscle and smooth muscle myosin light chain involved in cell motility, vascular regulation of inflammation, permeability, and apoptosis [36, 42, 43], with an important role in endothelial/epithelial barrier dysfunction and vascular leak, trademarks of ARDS. Direct sequencing of *MYLK* in

individuals of European and African descent with sepsis, sepsis-associated ARDS, and healthy controls identified 57 genetic variations and 51 polymorphic base substitutions. Five of ten *MYLK* SNPs conferred an amino acid change and four novel polymorphisms. Genotyping studies showed several *MYLK* SNPs to be overrepresented in Caucasians as well as several SNPs overrepresented in African Americans. These observations implicate a variety of potential contributors that may influence ARDS incidence and mortality. Recent reports support a genetic/epigenetic predisposition to ARDS, with several studies highlighting individual genetic variation as a contributor to ALI susceptibility with increased frequency of ARDS-associated variants in individuals with African descent. For example, the coding SNPs in *MYLK*, rare in European descendants but frequent in those of African descent, confer susceptibility to ARDS as well as severe asthma in African Americans [36].

## Chronic Comorbid Conditions Associated with ARDS Disparities

African American and Hispanic/Latino populations exhibit decreased life expectancy and disproportionately higher morbidity and mortality from preventable diseases [38, 44]. These include the burden of acute and chronic lung diseases, conditions well established to be significant and distributed unevenly across gender, ethnic, and social groups, including African Americans and Latinos [44]. A well-established Index of comorbidity, the Charlson Comorbidity Index (CCI), has been used to assess the comorbidities in ARDS patients. CCI has been statistically significantly correlated with the acute physiology and chronic health evaluation score, also known as APACHE II, and sequential organ failure assessment (SOFA) score ($r=0.387$, $p<0.01$ and $r=0.288$, $p<0.05$, respectively) [45]. The CCI score is determined through the sum of an already established point value for categories of comorbidities, where each condition category is scored from 1 to 6 (Table 7.1). Examination of the CCI list of comorbidities indicates there are several which are more common among racial and ethnic minorities. Chronic untreated conditions such as diabetes are more often seen in minorities and some of these conditions, such as diabetes, predispose to sepsis development [14]. African American septic patients are more likely to have diabetes, chronic renal failure, obesity, and HIV compared to whites (Table 7.3).

A retrospective cohort study analyzing 47 patients over 198.2 days (6.6 months) using CCI showed that the prognosis of ARDS was affected more by comorbidity than by age [45].

It has been estimated that the overall chronic disease prevalence will increase 42 % by 2023 and the projected economic burden will be about $4.2 trillion; that includes the economic cost associated with obesity, diabetes, and hypertension, conditions with higher prevalence among blacks and Hispanics [46]. Increasing access to interventions that enhance outcomes and care of individuals with chronic preexisting conditions may decrease ARDS incidence and improve its prognosis (Table 7.4).

**Table 7.3** Charlson Comorbidity Index (CCI)

| Points | Comorbidities |
|---|---|
| 1 | Dementia |
| | Peripheral vascular disease |
| | Myocardial infraction |
| | Congestive heart failure |
| | Ulcer disease |
| | Mild liver disease |
| | *Diabetes (without complications)* |
| | *Chronic pulmonary disease* |
| | Cerebrovascular disease |
| 2 | Lymphoma, multiple myeloma |
| | Leukemia |
| | *Diabetes (with end organ damage)* |
| | Hemiplegia |
| | Moderate or severe renal disease |
| | Second solid not metastatic tumor |
| 3 | Moderate or severe liver disease |
| 6 | Second solid metastatic tumor |
| | *AIDS* |

Comorbidities commonly found in minorities are italicized

**Table 7.4** Chronic disease: current and projected burden, USA, 2003–2023

| Chronic disease | Increase in prevalence (%) | Current cost (billion $) (2003) | Future cost (billion $) (2023) |
|---|---|---|---|
| Overall chronic illness | 42 | 271 | 814 |
| Diabetes | 53 | 132 | 430 |
| Pulmonary conditions | 31 | 139 | 384 |

*Source*: Adapted from Bodenheimer T et al. [46]

## Access to Care Effect on Disparities

Despite substantial evidence documenting racial and ethnic disparities in health care, the analysis of the factors involved in these disparities continues to be a challenging and complex process. Health status is intrinsically related to several factors, including health services use, socioeconomic status, physical environment, discrimination, racism, and literacy levels. These factors are known to be associated with race and ethnicity; furthermore, Black and Latino patients live in geographically segregated regions and use different hospitals than whites [25, 47]. The complex relationships between health and biology, genetics, and individual behavior likely contribute to ARDS disparities.

In the USA, health care access is a significant determinant of health status; particularly due to the way the health system is organized. The presence or absence of health insurance defines individual access to medical care and consequently health condition throughout life. Data from the National Healthcare Quality Report (NHQR) 2013 indicates that 26 % of Americans reported barriers that restricted their access to care. In addition to issues with health care access, disparities also exist with regard to quality of care, with Blacks and Hispanic/Latinos receiving decreased quality of health care compared to non-Hispanic whites. Most of these disparities of care related to race, ethnicity, or income have remained without any significant change over the past several years [16]. Uninsured individuals are less likely to have a regular source of care, are more likely to report delaying seeking care, and are more likely to report that they have not received needed care—all resulting in experiencing avoidable hospitalizations, emergency hospital care, and adverse health outcomes [17].

Data from Healthy People 2020 shows that delays in accessing or inability to obtain necessary medical care is directly related to the Federal Poverty Level (FPL) with Blacks and Hispanics disproportionately affected [48]. African Americans and Hispanics had lower odds of receiving pneumococcal vaccination, smoking cessation counseling, first antibiotic dose within 4 h of accessing the emergency room, and influenza vaccination [49]. Pneumococcal immunization and influenza immunization among hospitalized patients with pneumonia and long-stay nursing home residents are some of the several quality measures for prevention of pneumonia, a condition that is frequently associated with ARDS [16]. Alcohol abuse, which is commonly found in African Americans, Hispanics, and Native Americans, is associated with higher acuity of acute critical illnesses, as well as higher rates of sepsis, pancreatitis, ARDS, and organ dysfunction.

## Summary

Further ARDS research studies focused on Latinos are needed to improve the understanding of the ethnic differences and racial mixture present in minority groups. The American Thoracic Society (ATS) Executive Committee recognizes these disparities as one of the most important contributors to the health expenses in the health care system and has created a Health Equality Subcommittee with the purpose to direct efforts to eliminate respiratory health disparities. In order to address these inequities, efforts from multiple stakeholders, such as government, health care professionals, and other members of the society are required [49]. In addition, research efforts directed to better understand the genetic variation and environmental interaction among Latinos, African Americans, Native Americans, and other minorities are much needed in order to understand the multifactorial causes associated with disparities that predispose to critical illness and adverse outcomes. The health care system in the USA has entered into a transformation phase, with the Affordable Care Act offering the possibility to address the health care inequities and access among minorities thereby decreasing the impact of comorbid conditions that predispose and influence the course of critical care illnesses. In addition, the rapid growth in research focused on the genomic and epigenetic analysis of ARDS risk and outcomes in specific populations may allow integration with personalized medicine as part of routine medical care.

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