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In this issue a good reviews from Qatar and Saudi Arabia dealing with important issue for the nursing field in addition to research papers from Turkey, Lebanon and Australia.

Al Nassar., looked at the Extent of Childhood Obesity and the Scope of School-Based Health Promotion Interventions in Saudi Arabia through a Review of Literature. The author stressed that Childhood obesity is a concerning trend and represents one of the most significant challenges to public health worldwide. Childhood obesity in Saudi Arabia has become a significant concern for scholars and healthcare professionals. An extensive amount of research has been conducted to identify the most effective interventions to prevent childhood obesity in light of its prevalence, health consequences, and associated costs. Studies indicate that identifying and addressing obesity-related behaviours can be valuable for developing and implementing effective interventions and prevention measures to mitigate childhood obesity in Saudi Arabia. It has been shown that obesity-related behaviours can be changed through school-based health promotion interventions. Therefore, the present review summarises the current evidence on childhood obesity, including its prevalence, health consequences, and obesity-related behaviours in children and adolescents in Saudi Arabia. In addition, it aimed to determine the scope of school-based health promotion efforts in Saudi schools to reduce childhood obesity.

Hersi , looked at Barriers and Facilitators of Palliative Care for Adult Heart Failure Patients: Integrative Review. Heart failure (HF) patients usually experience symptoms such as dyspnea, tiredness, cognitive impairment, and pain. Those symptoms contribute to a decline in physical functioning and a limitation in their ability to do their daily tasks. Palliative care (PC) is crucial for people with HF because it focuses on improving the quality of life and can reduce symptoms and improve function. Qatar aims to introduce PC services for adult patients with HF. Objective: This integrative review aims to investigate the barriers, facilitators, and the outcomes to the provision of palliative care among adult patients with HF. Methods: Whittemore and Knafl's framework guided this integrative review. Using three databases, twenty (n=20) peer-reviewed articles, published between 2011 and 2022, were included in the integrative review. The Mixed Methods Appraisal Tool was used to assess the quality of these articles. The data was then extracted and thematically analyzed before being synthesized. Results: The barriers, facilitators, and outcomes of providing PC services to individuals with HF were identified from the perspectives of patients, healthcare providers, and healthcare organizations. Conclusion: Gaining a comprehensive understanding of these barriers, facilitators, and outcomes associated with providing PC services to adults with HF is central for the effective implementation of such services for this patient population in Qatar.

Dr Bahjat , discussed the conflict issues in Ghaza. He stressed that While the bombing of Gaza and the resulting loss of civilians continues, I urge the international community to stop the war now, protect civilians (including health-care workers), lift the 16-year blockade on Gaza immediately, and allow international aid to enter Gaza to support the health-care system that has already collapsed.

Helvaci, et al., discussed the Atherosclerotic background of digital clubbing in sickle cell diseases. They studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, $p>0.05$, respectively). Beside digital clubbing (14.8% vs 6.6%, $p<0.001$), smoking (23.8% vs 6.1%, $p<0.001$), alcohol (4.9% vs 0.4%, $p<0.001$), transfused red blood cells (RBCs) in their lives (48.1 vs 28.5 units, $p=0.000$), disseminated teeth losses (5.4% vs 1.4%, $p<0.001$), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, $p<0.001$), ileus (7.2% vs 1.4%, $p<0.001$), cirrhosis (8.1% vs 1.8%, $p<0.001$), leg ulcers (19.8% vs 7.0%, $p<0.001$), coronary heart disease (CHD) (18.0% vs 13.2%, $p<0.05$), chronic renal disease (CRD) (9.9% vs 6.1%, $p<0.05$), and stroke (12.1% vs 7.5%, $p<0.05$) were all higher, and autosplenectomy (50.4% vs 53.3%, $p<0.05$) and mean age of mortality were lower in males, significantly (30.2 vs 33.3 years, $p<0.05$). The authors concluded that the hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Parallel to digital clubbing, all of the atherosclerotic risk factors or consequences including smoking, alcohol, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, CHD, CRD, and stroke were higher, and autosplenectomy and mean age of mortality were lower in males which can not be explained by effects of smoking and alcohol alone at the relatively younger mean age. So autosplenectomy may be a good whereas male gender alone may be a bad prognostic factor, and digital clubbing may have an atherosclerotic background in SCDs.

# THE EXTENT OF CHILDHOOD OBESITY AND THE SCOPE OF SCHOOL-BASED HEALTH PROMOTION INTERVENTIONS IN SAUDI ARABIA: A REVIEW OF LITERATURE

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## Abstract

Childhood obesity is a concerning trend and represents one of the most significant challenges to public health worldwide. Childhood obesity in Saudi Arabia has become a significant concern for scholars and healthcare professionals. An extensive amount of research has been conducted to identify the most effective interventions to prevent childhood obesity in light of its prevalence, health consequences, and associated costs. Studies indicate that identifying and addressing obesity-related behaviours can be valuable for developing and implementing effective interventions and prevention measures to mitigate childhood obesity in Saudi Arabia. It has been shown that obesity-related behaviours can be changed through school-based health promotion interventions. Therefore, the present review summarises the current evidence on childhood obesity, including its prevalence, health consequences, and obesity-related behaviours in children and adolescents in Saudi Arabia. In addition, it aimed to determine the scope of school-based health promotion efforts in Saudi schools to reduce childhood obesity.

Keywords: Childhood Obesity, Overweight, Children, Adolescence, Health Promotion, School, Saudi Arabia

## Introduction

Childhood obesity is an emerging public health concern around the world. Over 340 million children and adolescents aged five to 19 were overweight or obese in 2016(‽1). Childhood obesity prevalence rates have climbed dramatically in developed and developing countries (‽2). In Saudi Arabia, childhood obesity has become a significant concern for scholars and healthcare professionals. According to WHO (‽3), the proportion of obese children between the ages of 5 and 18 has increased from 14.3% in 2010 to 17.4% in 2016. These percentages are particularly alarming, considering that children under 19 account for 30% to 35% of the Saudi Arabian population (‽4).

Several factors have contributed to the emergence of childhood obesity. The obesity epidemic has been attributed to urbanization and increased disposable income in both developed and developing countries (‽5). Saudi Arabia's economy has grown at one of the fastest rates (‽6). Saudi Arabia has also experienced rapid and massive urbanisation. According to the United Nations (‽7), urban residents in Saudi Arabia increased from approximately 20% in 1950 to about 80% in 2000 and are expected to reach about 90% by 2050. Consequently, family and individual lifestyles are changing rapidly in Saudi Arabia today, including physical activity behaviours, food preparation, marketing, and choices.

Significant attention has been paid to identifying the most effective interventions to prevent childhood obesity considering its prevalence, health consequences, and associated costs. Researchers claim that developing and implementing effective interventions and prevention measures to mitigate childhood obesity in Saudi Arabia can be achieved by identifying and addressing obesity-related behaviours (‽8,‽9). Additionally, school-based interventions were shown to change obesity-related behaviours (‽10); contributing to the reduction of childhood obesity. It has been found in a previous review that interventions and national programs are urgently needed in Saudi Arabia to combat the obesity epidemic plaguing the country, especially at the school level (‽11).

The present review summarises the current evidence on childhood obesity, including its prevalence, health consequences, and obesity-related behaviours among children and adolescents in Saudi Arabia. In addition, this literature review aimed to determine the scope of school-based health promotion efforts in Saudi Arabia to reduce childhood obesity.

## Methodology

Six electronic databases - Medline (EBSCO host), PsycINFO (EBSCO host), SPORTDiscus (EBSCO host), Education Research Complete (EBSCO host), EMBASE, and Web of Science - were searched to identify relevant published literature based on the following keywords: child/childhood/children AND obesity/overweight AND school-based intervention AND Saudi Arabia. Additionally, the study utilised data from government and non-government sources such as WHO and the KSA Ministry of Health. The Critical Appraisal Skills Programme (CASP) tool was used to evaluate sources' credibility. The search results were combined into an Endnote library (bibliographic software).

Inclusion criteria included (a) peer-reviewed studies published in Arabic or English between October 1, 2000, and October 31, 2023; (b) studies that evaluated the prevalence, obesity-related behaviours, and/or impact of overweight and/or obesity in Saudi Arabian children (aged five to 19 years); and/or (c) School-based health promotion interventions aimed at preventing and managing overweight and/or obesity. Exclusion criteria included (a) Studies that targeted preschool children (younger than five years old), college or university students, and young adults (b) studies that examined specific diseases related to obesity, such as metabolic syndrome (c) non-empirical findings, such as letters, conference proceedings, commentaries, or case reviews; (d) studies with interventions outside the school (e.g., community settings, at home, hospitals, and camps) or in a clinical setting; (e) duplicated studies or, if the same data set was used in several studies, one study was selected; (f) non-Saudi Arabian studies.

Two stages were followed to identify papers for inclusion in this literature review. During stage one, the author screens and selects titles and abstracts based on inclusion and exclusion criteria. In stage two, the author screens and selects full-text articles. The author retained the search results and repeated the search a few days later, reflecting on any discrepancies and resolving them as necessary. A particular interest lies in articles that discuss the prevalence rates, obesity-related behaviours, and the impact of childhood obesity in Saudi Arabia. In addition, articles address school-based health promotion interventions for overweight and obesity.

## The Literature Review

### Definitions of Overweight and Obesity in Children

Several definitions of the terms overweight and obesity in children and adolescents have been developed by various organisations, including the WHO, the CDC, the IOTF, and the Saudi MoH. Table 2.1 illustrates the Definition of Overweight and Obesity in Children Based on BMI Depending on the age group. These criteria yield different estimates of overweight and obesity prevalence.

BMI's effectiveness and limitations have been extensively discussed. BMI is calculated using the total body weight of the individual without taking into account lean (muscle) and fat mass (12). Obesity is characterized by an increase in body fat mass that poses a health risk. The regional distribution of body fat is also essential when assessing obesity-associated health problems (12). It is possible to estimate body fat and body fat distribution using simple methods such as WC, skinfold thickness, and waist-to-hip circumference ratio. Despite this, BMI is commonly used as a measure of obesity in both population-based studies and clinical practice, especially among children and adolescents. The CDC (13) recommends BMI as a screening tool for weight-related and health-related problems in children and adolescents. The CDC (13) also recommends further assessments such as skinfold thickness measurements, family history, eating patterns, and PA evaluations for individuals with high BMIs. It has been found that BMI charts are useful for assessing children's efforts to lose weight and can provide a reasonably accurate assessment of the change in body fat over time (14). As a result, to capture the extent of childhood obesity and all efforts made to promote health in school programs, lifestyle outcomes and BMI/BMI-Z have been included in this literature review. BMI z score measures how many standard deviations a child or young person's BMI is above or below the average BMI for their age and gender. Instead of using BMI, BMI z scores provide a direct comparison of BMI (and any changes in BMI) across different ages and genders.

### Epidemiological Features of Childhood Obesity in Saudi Arabia

In recent years, Saudi Arabia has experienced an alarming increase in obesity and overweight among children and adolescents, making it one of the Middle Eastern countries with the highest obesity rates (15). According to WHO's Global Health Observatory, in 2010, the prevalence of overweight and obesity among Saudi children (5-19 years old) was 31.6% and 14.3%, respectively (3). However, in 2016, the prevalence of overweight and obesity among Saudi children (5-19 years old) rose to 35.6% and 17.4%. Furthermore, based on national prevalence rates, El Mouzan et al. (16) estimated that 24% and 9% of Saudi children (5-18 years) were overweight and obese, respectively (WHO references). However, the rates were slightly lower when CDC references were applied. Furthermore, according to the same survey by El Mouzan (16), younger children (5-12 years old) had lower overweight and obesity rates than older children (13-18 years old), regardless of the references used for defining overweight and obesity.

**Table 1. Definition of Overweight and Obesity in Children Based on BMI**

| | Age Group | Overweight | Obesity |
|---|---|---|---|
| WHO Growth Charts | <5 years | Weight-for-height greater than two standard deviations above the median of the WHO Child Growth Standards | Weight-for-height greater than three standard deviations above the median WHO Child Growth Standards |
| | 5-19 years | BMI-for-age greater than one standard deviation above the median of the WHO Growth Reference. | Greater than two standard deviations above the median WHO Growth Reference |
| CDC Growth Charts | 2–20 years | BMI-for-age = 85th ≤ 95th percentile | BMI-for-age ≥ 95th percentile, or BMI ≥ 30 kg/m2 whichever is smaller |
| Saudi Growth Charts | 0–18 years | BMI-for-age percentile >85th ≤ 95th centile | BMI-for-age percentile >95th centile |
| IOTF | 2–18 years | Age- and sex-specific BMI cut-off points* correspond to an adult BMI of 25 kg/m2 | Age- and sex-specific BMI cut-off points* correspond to an adult BMI of 30 kg/m2 |

BMI= body mass index, WHO= World Health Organization, IOTF= International Obesity Task Force, CDC= US Centres for Disease Control, * For children younger than 2 years, the indicator is weight-for-length

Similarly, a survey of various regions that included young children found that 6% of children aged 2-6, 8% of children aged 6-13 and 11% of children aged 13-18 were obese (⁋17). The findings are consistent with other studies that report lower obesity rates among young children (⁋18,⁋19,⁋20,⁋21). However, the WHO data illustrate a different pattern, indicating that children 5–9 years of age have a higher prevalence of obesity than children 10–19 years of age (⁋3).

The prevalence of obesity among adolescents in Saudi Arabia was 6% based on CDC criteria and 9% based on WHO criteria based on a national survey published in 2010 (⁋16). In 2015, a national survey of 12,575 adolescents revealed that 16 % were obese and 14 % were overweight (⁋22), indicating that adolescents' obesity rate has increased (⁋16). However, another survey conducted in 2012 in seven regions of the country found that 11% of adolescents (13-18 years) were obese, compared with 25% who were overweight (⁋17). Nevertheless, this 2012 survey defined overweight as having a body mass index (BMI) of >85th centile without specifying how far overweight exceeds the 95th centile, indicating that 25% included both overweight and obesity (⁋17). Consequently, 14% of adolescents were overweight, excluding 11% who were obese, similar to the Al-Buhairan et al. study (⁋22). However, it should be noted that El Mouzan et al. (⁋17) conducted their study between 2004 and 2005 and did not include some of the more urbanised regions of Saudi Arabia, such as the western and eastern regions, where obesity and overweight rates are high. As an illustration, a study conducted in three major urbanised cities in Saudi Arabia (Riyadh, Jeddah, and Al Khobar) found a higher prevalence of obesity (19%) and overweight (20%) among adolescents (⁋23).

Overall, differences in the prevalence of overweight and obesity among Saudi children and adolescents may be partly explained by disparities in the definitions and regions from which the population was sampled. In turn, these differences have led to a high demand to unify the reference chart. This is to eliminate potential confusion in the definition of obesity and overweight in future studies.

## Health Impacts of Childhood Obesity in Saudi Arabia

Overweight and obesity were estimated to cause 39% of deaths among adults (four million deaths) worldwide in 2015 (⁋24). The WHO (⁋25) notes that several adult diseases originate in childhood, so prevention and treatment strategies should address children and adults.

Numerous studies have examined cardiometabolic risk factors in Saudi children (⁋26,⁋27,⁋28,⁋29); however, very few have examined these factors concerning overweight and obesity. Cardiometabolic risk encompasses many factors associated with developing type II DM and CVD (⁋30). Abdominal obesity, smoking, insulin resistance, high BP, high LDL-C, low HDL-C, high TG, high fasting blood glucose, and a disturbing inflammatory profile are important factors associated with increased cardiometabolic risk. Prevention or reduction of these risk factors can reduce the burden of non-communicable diseases, such as cardiovascular disease and type 2 diabetes (⁋30).

### *Cardiometabolic risk factors*

In a cross-sectional study of school children and adolescents from ten schools in Riyadh, the authors examined Saudi children's cardiometabolic risk and its relation to overweight, obesity, and lifestyle behaviours (⁋31). They reported that 51.5% of the children had elevated BP (>90th percentile), 13.6% had elevated TG >=1.1 mmol/L and 1% prevalence of elevated fasting blood glucose ( >= 6.1 mmol/L). The study reported an association between high BP and BMI quartiles and WC. They found that WC (>75th percentile, using CDC reference data) predicted elevated TG >= 1.1 mmol/L in Saudi children after adjusting for age, gender, and activity level (⁋31). Nevertheless, the results of this study should be interpreted cautiously due to a lack of information regarding whether single or multiple BP measurements were performed, whether the children were given time to rest before BP measurements, whether the left arm or right arm was used for measurement, and how PA was determined. Furthermore, a review of three studies among Saudi schoolboys in Riyadh reached similar conclusions regarding BP and TG levels (⁋32). Al-Hazzaa et al. (⁋32) found boys with >=25% fat (based on skinfold thickness) had significantly higher mean systolic and diastolic BP and TG levels. In addition, mean HDL-C concentrations were lower in boys with fat levels >25%, while total cholesterol levels did not differ.

Furthermore, Al-Daghri et al. (⁋26) explored the relationship between adiposity indices (BMI and WC) and metabolic and hormonal markers in Saudi children from Riyadh. It was found that overweight, obese, and normal children had significant differences in insulin resistance as measured by HOMA-IR, LDL-C, HDL-C, TG, and systolic and diastolic BP (⁋26). The results of the study revealed that children with a higher BMI have a lower HOMA-IR, indicating greater insulin resistance (⁋26). Similarly, a study was conducted to examine Vitamin D Deficiency and Cardiometabolic Risks among Saudi adolescents in Riyadh (⁋33). Based on the findings of the study, approximately 20% of adolescents had elevated blood glucose concentrations (>=5.6 mmol/L), over 60% had low HDL-C concentrations (<1.03 mmol/L), and 15% had elevated TG concentrations >= 1.7 mmol/L (⁋33). Additionally, over 30% of these adolescents were overweight or obese, with 10% having abdominal obesity (>92 cm in boys and >86 cm in girls). Overweight and obesity were not examined in relation to cardiometabolic risk factors in this study,; however, higher BMI in males was associated with lower serum 25-hydroxyvitamin D levels, which is indicative of inadequate vitamin D levels (⁋33).

Thus, these studies suggest that obesity may contribute to adverse cardiometabolic health in Saudi children. However, there has been scant research conducted in other regions of Saudi Arabia besides Riyadh, so it is

difficult to draw conclusions about children in other areas. This necessitates conducting a national survey similar to that conducted by Al-Buhairan et al. (22) to determine the health consequences of childhood obesity in Saudi Arabia.

### *Sleep-disorders*

Sleep-disordered breathing has also been linked to childhood obesity. It refers to sleep conditions in which the upper airway is blocked entirely or partially (34). Sleep-disordered breathing can affect a child's behavioural and emotional regulation, learning abilities, and alertness (35). In Saudi children, being overweight was positively associated with reported sleep disorders (36). Nevertheless, it is unclear how overweight status was measured or defined in this study, and the findings are based on parents' responses to a questionnaire determining sleep-disordered breathing. Therefore, objective methods of assessing sleep-disordered breathing, such as polysomnography, are required for Saudi children to provide more accurate results. Moreover, a cross-sectional study was conducted in three major Saudi Arabian cities (Al Khobar, Jeddah, and Riyadh) to determine the prevalence of short sleep duration and its association with obesity among adolescents between the ages of 15-19 years old (37). They reported that adolescents who were overweight or obese had a greater prevalence of short sleep duration than adolescents with a normal BMI, according to IOTF age- and sex-specific BMI cut-off reference standards. The same results were found in a study of young Saudi children (10-19 years of age) (38). In addition, more overweight and obese children reported intermittent rather than continuous sleep, suggesting lower sleep quality (38). Consequently, it can be concluded that short sleep duration and poor sleep quality have been implicated as risk factors and consequences of childhood obesity in Saudi Arabia.

### *Social and psychological consequences*

Concerns have been raised regarding the social and psychological consequences of childhood obesity. Approximately 45% of Saudi adolescents responded that they needed to lose weight, indicating a negative body image (39). Compared to adolescents who reported feeling satisfied with their bodies, these adolescents were more likely to feel sad and hopeless. While there has been no study on bullying in Saudi Arabia regarding obesity or overweight, bullying rates in Saudi schools are high. A national survey of Saudi adolescents found that 27% of males and 23% of females had experienced bullying within the past 30 days before the survey was conducted (22). The result is higher than the 21% reported by US adolescents (40) and higher than the 19% reported by Australian children and adolescents (41). However, these differences in the prevalence of bullying in children may result from differences in the definition of bullying and the methods for measuring it. Despite the lack of studies assessing the relationship between bullying and overweight and obesity in Saudi Arabia, Ottova et al. (42) found that overweight children from ten European countries scored significantly lower on the social acceptance and bullying dimensions, suggesting that these dimensions of health-related quality of life are impaired in comparison with children and adolescents of normal weight. Furthermore, a meta-analysis of cross-sectional studies reported that bullying victimisation was associated with an increased likelihood of being overweight or obese (43). Nevertheless, most studies rely on cross-sectional designs, which makes it difficult to determine whether bullying is a cause or a consequence of obesity in children.

## Obesity-Related Behaviour among Children and Adolescents in Saudi Arabia

Identifying risk factors is a crucial first step in reducing the burden of excessive body weight among vulnerable age groups in Saudi Arabia (8,9). Although genetic factors contribute to obesity, they are unlikely to explain the rapid increase in obesity rates in Saudi Arabia (28). Saudi Arabia has undergone numerous changes since the 1980s, including economic and social developments, such as the increasing number of women entering the workplace, which has improved the standard of living for the population. However, this positive lifestyle change has also been associated with increased physical inactivity and overweight/obesity rates (44). Given the complexity and multifaceted nature of obesity, properly identifying modifiable risk factors is crucial to combating obesity prevalence in Saudi Arabia. Several obesity-modifiable risk factors have been examined in Saudi Arabian studies, including PA, SB, and dietary habits.

### *Physical Activity*

It is well-proven that regular PA benefits children and adolescents. It can improve cardio-respiratory fitness, weight control, self-esteem, and psychological well-being and reduce the risk of chronic diseases such as DM, stress, anxiety, and depression (45). In contrast, a lack of PA can lead to an energy imbalance (less energy expended than consumed through diet) and may increase the probability of becoming overweight or obese (46). This has also been observed in Saudi Arabia. For example, according to a study conducted in the Qassim region, children who engage in sports activities two hours a day are less likely to become overweight (20). Similarly, a study of students (15-19 years old) in the eastern region found a negative correlation between BMI and PA among males and a negative correlation between WC and reported PA among males and females (44). However, a study in Makkah that included girls only (8–11 years) found no significant relationship between the average number of daily steps (measured using an accelerometer) and BMI categories (47). Additionally, AL Kutbe et al. (47) reported that less than 10% of the participants achieved the recommended 10,000–12,000 steps daily. It has been suggested that living in the desert, where summers are extremely hot, and winters are very cold and windy, could contribute to reduced PA levels. In addition, a lack of facilities and equipment for exercise may also be a contributing factor. According to Mahfouz et al. (28), a lack of PA in class was also associated with an increased likelihood of obesity

among students. While several studies have examined PA as a risk factor for obesity among Saudi children, there is a lack of emphasis on the role of schools in providing PA.

### *Dietary Habits*

Economic development has resulted in significant changes in food consumption patterns and eating habits in Saudi Arabia. Eating has evolved from a simple source of nourishment to a lifestyle marker and source of pleasure (48). In Saudi Arabia, several studies have examined diet as a risk factor for obesity. For instance, in a study conducted in Riyadh, 21% of adolescents did not consume fruits and vegetables daily, and 32% did not exercise on a regular basis (49). Despite this, there was no significant correlation between students' BMIs and their lifestyles or eating habits. In contrast, a study conducted on children in the Qassim region found that children who ate restaurant food twice a week were twice as likely to become overweight (20). Furthermore, it was found that children from Riyadh (12-16 years old) who consume sugary drinks have a higher BMI (50). These findings are similar to those of a study conducted in Makkah on girls between 8 and 11 (47). In addition, breakfast, fruit, and milk consumption by obese Saudi children was lower than that of non-obese Saudi children (51).

The consumption of unhealthy snacks and sugar-sweetened beverages is prevalent among adolescents and young adults in Saudi Arabia (52). However, a contradictory association was found between consuming sweets and sugar-sweetened beverages and childhood obesity in Saudi Arabia. Several epidemiological studies reported that sweets consumption was associated with weight loss in children (53,54), while a few studies reported that sweets consumption was associated with weight gain in children (55). The results of a systematic review examining several cohort studies and randomised controlled trials indicated that sugar-sweetened beverages might contribute to weight gain among children and adolescents (56). The contradictory results may be explained by the fact that sugar-sweetened drinks are commonly served alongside meals. Consequently, children consume more calories and are more likely to become overweight and obese. In contrast, sweets are usually consumed between meals. In turn, this may reduce children's appetites for lunch and dinner, reducing their calorie intake.

It has been demonstrated that eating a large breakfast can reduce obesity risk. An interventional study showed that people who consume a large breakfast are more likely to lose weight and reduce their WC than those who consume a large dinner (57), while skipping breakfast significantly impacts BMI and WC (58). However, the prevalence of skipping breakfast among children and adolescents in Saudi Arabia varies. This is because cultural norms may differ from region to region. In Abha, 72% of children between the ages of 8 and 18 consume breakfast frequently, while 28% do not (59). In contrast, a study in Jeddah found that more than half (54%) of the sample children did not consume breakfast (60). More urban areas were also associated with healthier dietary behaviours (61). In this regard, it is necessary to develop a program tailored to the needs of Saudi Arabia's different regions.

### *Sedentary Behaviours*

Saudis' socioeconomic status has changed significantly since the oil discovery in Saudi Arabia (62). Although it has benefitted the region, people's lifestyles have become more sedentary. For instance, most Saudi children use cars for transportation to and from school, play video games, watch television for extended periods, and play less in open fields (63). Additionally, SB has been linked to childhood obesity in Saudi Arabia. It has been found that obese Saudi children are less active than their non-obese counterparts (51). Similar results have also been found in another region (64). Television viewing and the use of electronic devices are also associated with childhood obesity in Saudi Arabia. The results of a case-control study of children (9-14 years old) in Riyadh city indicate that watching television at the weekend is associated with a higher risk of obesity (65). Furthermore, the study found that children with obesity were more likely to watch television at night. In contrast, children whose mothers determined how much television they could watch were less likely to be obese (65). Furthermore, children (12-16 years of age) who reported watching television more than two hours a day had a higher BMI than those who reported watching television less than one hour a day (50). A similar study reported that children (2-18 years of age) who spent two hours daily on electronic devices had a higher BMI (66). The authors claimed that watching television can lead to obesity and overweight by reducing PA and increasing food intake (66).

## Health Promotion to Combat Childhood Obesity in Saudi Arabia

### *General Health Promotion Approach*

The Ottawa Charter defines health promotion as empowering individuals to have greater control over their health (67). Therefore, health promotion is considered an essential element of public health practice and can be applied anywhere in the world. Various strategies are used for planning, developing, implementing, and evaluating health promotion policies and interventions. These include health education, mass media, community development and community engagement processes, advocacy and lobbying strategies, social marketing, health policy, and structural and environmental strategies (68). However, the study asserts that it is vital to consider local settings and social and cultural factors to implement these principles effectively (68). Setting approaches have their roots in WHO's Health for All initiative and, more specifically, the Ottawa Charter for Health Promotion. The fundamental principles of Healthy Settings include community participation, partnership,

empowerment, and equity. There have been numerous ways in which Healthy Setting approaches have been implemented, including in health-promoting schools.

### Health Promotion in the Saudi Context

Health promotion activities must be developed within Islamic rules to appeal to the Saudi population (69). It is, therefore, necessary to incorporate cultural and social norms when designing interventions for the Saudi community to avoid conflicts between health messages and sociocultural values. In the Saudi lifestyle, sociocultural values play an essential role, and excluding them may result in the ineffective implementation of any health promotion strategies (70). An example of this can be observed from a joint educational initiative operated between a British and a Saudi Arabian university, which indicated that religious beliefs have a positive influence on several aspects of women's health behaviours, including breastfeeding, birth spacing, eating habits, and condemning cigarettes and alcohol consumption (70), as these behaviours follow Islamic law. Furthermore, children's behaviour can also be changed by using culturally appropriate strategies, which have proven effective in other cultures. For example, Marlow et al. (71) stated that culturally relevant education led to an improvement in the eating habits and PA of adolescents on an Indian reservation in Nebraska, USA. Four children conducted a half-day workshop that encouraged behavioural adaptations by telling native American stories and engaging in activities (71). Thus, culturally appropriate strategies should be adopted to create positive behavioural changes in Saudi Arabia.

#### *School Settings in Health Promotion*

In the past three decades, several international initiatives have recognised and supported the role of schools in promoting and improving the population's health. For example, the WHO established a Global School Health Initiative in 1995, commonly known as 'Health Promoting Schools'. Children spend 40% of their waking hours at school, making it an appropriate place to implement obesity prevention interventions (72,73). In addition, the significant amount of time spent in schools can contribute to adopting a healthy lifestyle in the young population. This is because schools can provide children with the knowledge, attitudes, and skills needed to learn healthy behaviours through school health programs (74). In addition to improving academic performance, schools significantly impact students' health and social outcomes (75). Schools provide full contact, teach health education, provide meals, and model health-promoting settings that can assist in reducing obesity-related behaviours (76). Additionally, school-based interventions can benefit all students, regardless of their socioeconomic status (77), thus overcoming potential health inequalities (78).

In Saudi Arabia, schools and educational institutions play a significant role in improving the health status of the community (23). According to Al-Shehri et al. (79), approximately seven million students are enrolled in schools and colleges in Saudi Arabia. In recognition of schools' crucial role in promoting and improving population health, particularly in combating childhood obesity, the Saudi MoH has launched several initiatives. For example, in 2017, the MoH and the MoE launched a joint initiative named Rashaka (an Arabic word for fitness) to combat obesity among school children in Saudi Arabia (80). This initiative aims to promote a healthy lifestyle by improving dietary behaviour and increasing PA. The initiative was intended to run in four phases, and the fourth phase was scheduled to begin in 2020. Nevertheless, the pandemic and school closure hampered the initiative's prospects. This initiative screened 4,000 schools in 20 regions throughout Saudi Arabia (80). However, to our knowledge, no study has been conducted to determine the effectiveness of the (Rashaka) initiative in reducing obesity and overweight prevalence or whether obesity-related behaviours have changed among school children.

Research on school-based health promotion interventions targeting childhood obesity is lacking in Saudi Arabia (81,82,83). However, these studies have yielded mixed results regarding the effectiveness of school-based interventions. Notably, each of these studies employed a different method. This suggests that further research is needed to identify the most effective school-based interventions for reducing childhood obesity.

Nevertheless, several systematic reviews and meta-analyses have shown that school-based interventions positively influence children's obesity-related behaviour and/or BMI, including those conducted by (84,85,86,87). It is noteworthy that none of the reviews addressed Saudi Arabia. Since interventions must be aligned with the country's Islamic framework and sociocultural values, which set it apart from other countries, it is essential to evaluate the effectiveness of school-based interventions for obesity prevention and management in Saudi Arabia and to define the characteristics of the most effective intervention in reducing childhood obesity. This will enable policy makers to make use of theses interventions at the national level in order to mitigate childhood obesity.

## Conclusion and Recommendations

This literature review attempts to interpret and synthesise data to comprehend the extent, nature, and effects of childhood obesity, and the implementation of school-based health promotion programs in Saudi Arabia to mitigate the problem. The review focuses on quantitative and qualitative studies and includes data gathered from international organisations. According to the findings, childhood obesity has been a subject of considerable scholarly interest in Saudi Arabia. Most studies in this area are conducted using a cross-sectional survey. These studies have revealed the severity of the obesity problem, which has prompted action from healthcare agencies and public institutions. School-based health promotion programs could significantly contribute to the reduction of obesity. Further studies on school-based

health promotion programs to prevent obesity in Saudi children and adolescents are needed. Such studies should incorporate improved methodologies and consider prior experience when developing evidence-based interventions. Randomized controlled trials are necessary to determine the effectiveness of such interventions, as they provide the most reliable data. Furthermore, studies should include long-term follow-up to evaluate the long-term effects of school-based interventions. Ultimately, this could lead to better interventions that effectively combat childhood obesity in Saudi children and adolescents.

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**Conflict of Interests**

The author declares that there is no conflict of interest.

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# ATHEROSCLEROTIC BACKGROUND OF DIGITAL CLUBBING IN SICKLE CELL DISEASES

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## Abstract

**Background:** Sickle cell diseases (SCDs) are inborn and catastrophic processes on vascular endothelium, particularly at the capillaries.

**Methods:** All patients were included.

**Results:** We studied 222 males and 212 females with similar mean ages (30.8 vs 30.3 years, p>0.05, respectively). Beside digital clubbing (14.8% vs 6.6%, p<0.001), smoking (23.8% vs 6.1%, p<0.001), alcohol (4.9% vs 0.4%, p<0.001), transfused red blood cells (RBCs) in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), chronic obstructive pulmonary disease (COPD) (25.2% vs 7.0%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), coronary heart disease (CHD) (18.0% vs 13.2%, p<0.05), chronic renal disease (CRD) (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher, and autosplenectomy (50.4% vs 53.3%, p<0.05) and mean age of mortality were lower in males, significantly (30.2 vs 33.3 years, p<0.05).

**Conclusion:** The hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Parallel to digital clubbing, all of the atherosclerotic risk factors or consequences including smoking, alcohol, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, CHD, CRD, and stroke were higher, and autosplenectomy and mean age of mortality were lower in males which can not be explained by effects of smoking and alcohol alone at the relatively younger mean age. So autosplenectomy may be a good whereas male gender alone may be a bad prognostic factor, and digital clubbing may have an atherosclerotic background in SCDs.

**Key words:** Sickle cell diseases, hardened red blood cells, capillary endothelial damage, capillary endothelial edema, sudden deaths, atherosclerosis, digital clubbing

## Introduction

Chronic endothelial damage may be the main underlying cause of aging and death by causing end-organ failures (1). Much higher blood pressures (BPs) of the afferent vasculature may be the chief accelerating factor by causing recurrent injuries on vascular endothelium. Probably, whole afferent vasculature including capillaries are mainly involved in the destructive process. Thus the term of venosclerosis is not as famous as atherosclerosis in the literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic natures which eventually reduce blood flow to the terminal organs, and increase systolic and decrease diastolic BPs further. Some of the well-known accelerating factors of the harmful process are physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, overweight, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), stroke, peripheric artery disease (PAD), mesenteric ischemia, osteoporosis, dementia, early aging, and premature death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of obesity, HT, DM, cirrhosis, COPD, CRD, CHD, stroke, PAD, mesenteric ischemia, osteoporosis, aging, and dementia-like end-organ insufficiencies, the endothelial changes can not be reversed due to their fibrotic natures, completely. The accelerating factors and terminal consequences of the harmful process are researched under the titles of metabolic syndrome, aging syndrome, and accelerated endothelial damage syndrome in the literature (4-6). Similarly, sickle cell diseases (SCDs) are highly destructive processes on vascular endothelium initiated at birth, and terminated with an advanced atherosclerosis-induced end-organ failures in much earlier ages of life (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBCs). Probably loss of elasticity instead of shape is the major problem because sickling is rare in peripheric blood samples of the patients with associated thalassemia minors (TMs), and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present even at birth, but exaggerated with inflammations, infections, and emotional stress of the body. The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis terminate with disseminated tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, SCDs keep vascular endothelium particularly at the capillaries which are the actual distributors of the sickled or just hardened RBCs into the tissues (10, 11). The sickled or just hardened RBCs-induced chronic endothelial damage builds up an advanced atherosclerosis in much earlier ages of life. Vascular narrowings and occlusions-induced tissue ischemia and end-organ failures are the terminal results, so the life expectancy is decreased by 25 to 30 years for both genders in the SCDs (8).

## Material and methods

The clinical study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients of the SCDs were included. The SCDs are diagnosed with the hemoglobin electrophoresis performed by means of high performance liquid chromatography (HPLC). Smoking and alcohol habits, acute painful crises per year, transfused units of RBCs in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Cases with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the same Internist, and patients with disseminated teeth losses (<20 teeth present) were detected. Patients with an acute painful crisis or any other inflammatory process were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, marker of human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves, and to measure systolic BPs of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips was performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated TMs were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC, becuase the SCDs with associated TMs show a milder clinic than the sickle cell anemia (SCA) (Hb SS) alone (13). Systolic BPs of the pulmonary artery of 40 mmHg or higher are accepted as pulmonary hypertension (PHT) (14). The criterion for diagnosis of COPD is a post-bronchodilator forced expiratory volume in one second/forced vital capacity of lower than 70% (15). Acute chest syndrome (ACS) is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of 1.3 mg/dL or greater in males and 1.2 mg/dL or greater in females. Cirrhosis is diagnosed with physical examination, laboratory parameters, and ultrasonographic findings. Clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter of greater than 1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is performed for the cases with exercise electrocardiogram positivity. So CHD is diagnosed either angiographically or with the Doppler echocardiographic findings as movement

disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT. Sickle cell retinopathy is diagnosed with ophthalmologic examination in cases with visual complaints. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were the methods of statistical analyses.

## Results

The study included 222 males and 212 females with similar ages (30.8 vs 30.3 years, p>0.05, respectively). Prevalences of associated TMs were similar in both genders, too (72.5% vs 67.9%, p>0.05, respectively). Smoking (23.8% vs 6.1%) and alcohol (4.9% vs 0.4%) were higher in males (p<0.001 for both) (Table 1). On the other hand, transfused RBCs in their lives (48.1 vs 28.5 units, p=0.000), disseminated teeth losses (5.4% vs 1.4%, p<0.001), COPD (25.2% vs 7.0%, p<0.001), ileus (7.2% vs 1.4%, p<0.001), cirrhosis (8.1% vs 1.8%, p<0.001), leg ulcers (19.8% vs 7.0%, p<0.001), digital clubbing (14.8% vs 6.6%, p<0.001), CHD (18.0% vs 13.2%, p<0.05), CRD (9.9% vs 6.1%, p<0.05), and stroke (12.1% vs 7.5%, p<0.05) were all higher, and autosplenectomy (50.4% vs 53.3%, p<0.05) and mean age of mortality were lower in males (30.2 vs 33.3 years, p<0.05) (Table 2). Beside that the mean ages of terminal consequences were shown in Table 3.

**Table 1: Characteristic features of sickle cell patients**

| Variables | Males | *p*-value | Females |
|---|---|---|---|
| Prevalence | 51.1% (222) | Ns* | 48.8% (212) |
| Mean age (year) | 30.8 ± 10.0 (5-58) | Ns | 30.3 ± 9.9 (8-59) |
| Associated TMs† | 72.5% (161) | Ns | 67.9% (144) |
| ***Smoking*** | ***23.8% (53)*** | ***<0.001*** | ***6.1% (13)*** |
| ***Alcohol*** | ***4.9% (11)*** | ***<0.001*** | ***0.4% (1)*** |

*Nonsignificant (p>0.05) †Thalassemia minors

**Table 2: Associated pathologies of sickle cell patients**

| Variables | Males | p-value | Females |
|---|---|---|---|
| Painful crises per year | 5.0 ± 7.1 (0-36) | Ns* | 4.9 ± 8.6 (0-52) |
| ***Transfused units of RBCs†*** | ***48.1 ± 61.8 (0-434)*** | ***0.000*** | ***28.5 ± 35.8 (0-206)*** |
| ***Disseminated teeth losses (<20 teeth present)*** | ***5.4% (12)*** | ***<0.001*** | ***1.4% (3)*** |
| ***COPD‡*** | ***25.2% (56)*** | ***<0.001*** | ***7.0% (15)*** |
| ***Ileus*** | ***7.2% (16)*** | ***<0.001*** | ***1.4% (3)*** |
| ***Cirrhosis*** | ***8.1% (18)*** | ***<0.001*** | ***1.8% (4)*** |
| ***Leg ulcers*** | ***19.8% (44)*** | ***<0.001*** | ***7.0% (15)*** |
| ***Digital clubbing*** | ***14.8% (33)*** | ***<0.001*** | ***6.6% (14)*** |
| ***CHD§*** | ***18.0% (40)*** | ***<0.05*** | ***13.2% (28)*** |
| ***CRD¶*** | ***9.9% (22)*** | ***<0.05*** | ***6.1% (13)*** |
| ***Stroke*** | ***12.1% (27)*** | ***<0.05*** | ***7.5% (16)*** |
| PHT** | 12.6% (28) | Ns | 11.7% (25) |
| ***Autosplenectomy*** | ***50.4% (112)*** | ***<0.05*** | ***53.3% (113)*** |
| DVT*** and/or varices and/or telangiectasias | 9.0% (20) | Ns | 6.6% (14) |
| Rheumatic heart disease | 6.7% (15) | Ns | 5.6% (12) |
| Avascular necrosis of bones | 24.3% (54) | Ns | 25.4% (54) |
| Sickle cell retinopathy | 0.9% (2) | Ns | 0.9% (2) |
| Epilepsy | 2.7% (6) | Ns | 2.3% (5) |
| ACS**** | 2.7% (6) | Ns | 3.7% (8) |
| Mortality | 7.6% (17) | Ns | 6.6% (14) |
| ***Mean age of mortality (year)*** | ***30.2 ± 8.4 (19-50)*** | ***<0.05*** | ***33.3 ± 9.2 (19-47)*** |

*Nonsignificant (p>0.05) †Red blood cells ‡Chronic obstructive pulmonary disease §Coronary heart disease ¶Chronic renal disease **Pulmonary hypertension ***Deep venous thrombosis ****Acute chest syndrome

**Table 3: Mean ages of consequences of sickle cell patients**

| Variables | Mean age (year) |
|---|---|
| Ileus | 29.8 ± 9.8 (18-53) |
| Hepatomegaly | 30.2 ± 9.5 (5-59) |
| ACS* | 30.3 ± 10.0 (5-59) |
| Sickle cell retinopathy | 31.5 ± 10.8 (21-46) |
| Rheumatic heart disease | 31.9 ± 8.4 (20-49) |
| Autosplenectomy | 32.5 ± 9.5 (15-59) |
| Disseminated teeth losses (<20 teeth present) | 32.6 ± 12.7 (11-58) |
| Avascular necrosis of bones | 32.8 ± 9.8 (13-58) |
| Epilepsy | 33.2 ± 11.6 (18-54) |
| Priapism | 33.4 ± 7.9 (18-51) |
| Left lobe hypertrophy of the liver | 33.4 ± 10.7 (19-56) |
| Stroke | 33.5 ± 11.9 (9-58) |
| COPD† | 33.6 ± 9.2 (13-58) |
| PHT‡ | 34.0 ± 10.0 (18-56) |
| Leg ulcers | 35.3 ± 8.8 (17-58) |
| Digital clubbing | 35.4 ± 10.7 (18-56) |
| CHD§ | 35.7 ± 10.8 (17-59) |
| DVT¶ and/or varices and/or telangiectasias | 37.0 ± 8.4 (17-50) |
| Cirrhosis | 37.0 ± 11.5 (19-56) |
| CRD** | 39.4 ± 9.7 (19-59) |

*Acute chest syndrome †Chronic obstructive pulmonary disease ‡Pulmonary hypertension §Coronary heart disease ¶Deep venous thrombosis **Chronic renal disease

## Discussion

Acute painful crises are the most disabling symptoms of the SCDs. Although some authors reported that pain itself may not be life threatening directly, infections, medical or surgical emergencies, or emotional stress are the most common precipitating factors of the crises (19). Although the sickled or just hardened RBCs-induced capillary endothelial damage, inflammation, and edema are present even at birth, the increased basal metabolic rate during such stresses aggravates the sickling and capillary endothelial damage, inflammation, and edema, and may terminate with disseminated tissue hypoxia and multiorgan failures-induced sudden deaths in the SCDs (20). So the risk of mortality is much higher during the crises. Actually, each crisis may complicate with the following crises by leaving some sequelaes on the capillary endothelial system all over the body. After a period of time, the sequelaes may terminate with sudden end-organ failures and death during a final acute painful crisis that may even be silent, clinically. Similarly, after a 20-year experience on such patients, the deaths seem sudden and unexpected events in the SCDs. Unfortunately, most of the deaths develop just after the hospital admission, and majority of such cases are without hydroxyurea therapy (21). Rapid RBCs supports are usually life-saving for such patients, although preparation of RBCs units for transfusion usually takes time. Beside that RBCs supports in emergencies become much more difficult in such terminal patients due to the repeated transfusions-induced blood group mismatch. Actually, transfusion of each unit of RBCs complicates the following transfusions by means of the blood subgroup mismacth. Due to the significant efficacy of hydroxyurea therapy, RBCs transfusions should be kept just for acute events and emergencies in the SCDs (22). According to our experiences, simple and repeated transfusions are superior to RBCs exchange in the SCDs (23). First of all, preparation of one or two units of RBCs suspensions in each time rather than preparation of six units or higher provides time to clinicians to prepare more units by preventing sudden death of such high-risk cases. Secondly, transfusions of one or two units of RBCs suspensions in each time decrease the severity of pain and relax anxiety of the patients and their relatives because RBCs transfusions probably have the strongest analgesic effects during such crises. Actually, the decreased severity of pain by transfusions also indicates the decreased severity of inflammation in whole body. Thirdly, transfusions of lesser units of RBCs suspensions in each time by means of the simple transfusions decrease transfusions-related complications including infections, iron overload, and blood group mismatch. Fourthly, transfusions of RBCs suspensions in the secondary health centers prevent some deaths developed during the transport to the tertiary centers for the exchange. Finally, cost of the simple and repeated transfusions on insurance system is much lower than the exchange that

needs trained staff and additional devices. On the other hand, pain is the result of complex and poorly understood interactions between RBCs, white blood cells (WBCs), platelets (PLTs), and endothelial cells, yet. Whether leukocytosis contributes to the pathogenesis by releasing cytotoxic enzymes is unknown. The adverse actions of WBCs on the capillary endothelium are of particular interest with regard to the cerebrovascular diseases in the SCDs. For instance, leukocytosis even in the absence of an infection was an independent predictor of the severity of the SCDs, and it was associated with the higher risk of stroke (24). Disseminated tissue hypoxia, releasing of inflammatory mediators, bone infarctions, and activation of afferent nerves may take role in the pathophysiology of the intolerable pain. Because of the severity of pain, narcotic analgesics are usually required to control them (25), but according to our long term experience, simple and repeated RBCs transfusions are much more effective than the narcotics to control the intolerable pain in the SCDs.

Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCDs (26). It is an orally-administered, cheap, safe, and effective drug, and it may be the only life-saving drug in the treatment of the SCDs (27, 28). It interferes with the cell division by blocking the formation of deoxyribonucleotides via inhibition of ribonucleotide reductase. The deoxyribonucleotides are the building blocks of DNA. Hydroxyurea mainly affects hyperproliferating cells. Although the action way of hydroxyurea is thought to be the increase in gamma-globin synthesis for fetal hemoglobin (Hb F), its main action may be the prevention of leukocytosis and thrombocytosis by blocking the DNA synthesis (29, 30). By this way, the inborn inflammatory and destructive process of the SCDs is suppressed with some extent. Due to the same action way, hydroxyurea is also used in moderate and severe psoriasis to suppress hyperproliferating skin cells. As also seen in the viral hepatitis cases, although presence of a continuous damage of sickled or just hardened RBCs on the capillary endothelium, the severity of destructive process may be exaggerated by the patients' own WBCs and PLTs. So suppression of proliferation of the WBCs and PLTs may limit the capillary endothelial damage, inflammation, edema, tissue ischemia, and end-organ failures in the body (31). Similarly, final Hb F levels in the hydroxyurea users did not differ from their pretreatment levels (32). The Multicenter Study of Hydroxyurea (MSH) studied 299 severely affected adults with the SCA, and compared the results of patients treated with hydroxyurea or placebo (33). The study particularly researched effects of hydroxyurea on the painful crises, ACS, and requirement of RBCs transfusion. The outcomes were so overwhelming in the favour of hydroxyurea that the study was terminated after 22 months, and hydroxyurea was started for all patients. The MSH also demonstrated that patients treated with hydroxyurea had a 44% decrease in hospitalizations (33). In multivariable analyses, there was a strong and independent association of lower neutrophil counts with the lower crisis rates (33). But this study was performed just in severe SCA cases alone, and the rate of painful crises was decreased from 4.5 to 2.5 per year (33). Whereas we used all subtypes of the SCDs with all clinical severity, and the rate of painful crises was decreased from 10.3 to 1.7 per year ($p<0.000$) with an additional decreased severity of them (7.8/10 vs 2.2/10, $p<0.000$) (28). Parallel to our results, adults using hydroxyurea therapy for frequent painful crises appear to have a reduced mortality rate after a 9-year follow-up period (34). The complications start to be seen even in infancy in the SCDs. For instance, infants with lower hemoglobin values were more likely to have higher incidences of clinical events such as ACS, acute painful crises, and lower neuropsychological scores, and hydroxyurea reduced the incidences of them (35). Hydroxyurea therapy in early years of life may improve growth, and prevent end-organ failures. Transfusion programmes can also reduce all of the complications, but transfusions carry many risks including infections, iron overload, and development of allo-antibodies causing subsequent transfusions difficult. On the other hand, elevations of liver enzymes during some acute painful crises can not be reversed by withdrawing of the hydroxyurea therapy alone, instead withdrawal of all of the medications were highy effective in such cases during the 20-year experience on such patients. After normalization of the liver enzymes, the essential medications must be started one by one, instead of all of them at the same time, again. Thus hydroxyurea must even be used during the acute painful crises. Additionally, we observed mild, moderate, or even severe bone marrow suppressions and pancytopenia in some patients using high-dose hydroxyurea (35 mg/kg/day). Interestingly, such cases were completely silent other than some signs and symptoms of anemia, and all of them were resolved completely just by giving a few-day break for the hydroxyurea therapy and starting with smaller doses again.

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce inflammation and acute thromboembolic events. Although aspirin has similar anti-inflammatory effects with the other NSAIDs, it also suppresses the normal functions of PLTs, irreversibly. This property causes aspirin being different from other NSAIDs, which are reversible inhibitors. Aspirin acts as an acetylating agent where an acetyl group is covalently attached to a serine residue in the active site of the cyclooxygenase (COX) enzyme. Aspirin's ability to suppress the production of prostaglandins (PGs) and thromboxanes (TXs) is due to its irreversible inactivation of the COX enzyme required for PGs and TXs synthesis. PGs are the locally produced hormones with some diverse effects, including the transmission of pain into the brain and modulation of the hypothalamic thermostat and inflammation. TXs are responsible for the aggregation of PLTs to form blood clots. In another definition, low-dose aspirin use irreversibly blocks the formation of $TXA_2$ in the PLTs, producing an inhibitory effect on the PLT aggregation during whole lifespan of the affected PLTs (8-9 days). Since PLTs do not have nucleus and DNA, they are unable to synthesize new COX enzyme once aspirin inhibited the enzyme. The antithrombotic property of aspirin is

useful to reduce the incidences of myocardial infarction, transient ischemic attack, and stroke (36). Heart attacks are caused primarily by blood clots, and low dose of aspirin is seen as an effective medical intervention to prevent a second myocardial infarction (37). According to the medical literature, aspirin may also be effective in prevention of colorectal cancers (38). On the other hand, aspirin has some side effects including gastric ulcers, gastric bleeding, worsening of asthma, and Reye syndrome in childhood and adolescence. Reye syndrome is a rapidly worsening brain disease (39). The first detailed description of Reye syndrome was in 1963 by an Australian pathologist, Douglas Reye (40). The syndrome mostly affects children, but it can only affect fewer than one in a million children a year (40). It usually starts just after recovery from a viral infection, such as influenza or chicken pox (40). Symptoms of Reye syndrome may include personality changes, confusion, seizures, and loss of consciousness (39). Although the liver toxicity typically occurs in the syndrome and the liver is enlarged in most cases, jaundice is usually not seen with it (39). Early diagnosis improves outcomes, and treatment is supportive. Mannitol may be used in cases with the brain swelling (40). Although the death occurs in 20-40% of patients, about one third of survivors get a significant degree of brain damage (39). Interestingly, about 90% of cases in children are associated with an aspirin use (41). Due to the risk of Reye syndrome, the US Food and Drug Administration recommends that aspirin or aspirin-containing products should not be prescribed for febrile patients under the age of 16 years (42). Eventually, the general recommendation to use aspirin in children has been withdrawn, and it was only recommended for Kawasaki disease (39). When aspirin use was withdrawn for children in the US and UK in the 1980s, a decrease of more than 90% of Reye syndrome was seen (40). Due to the higher side effects of corticosteroids in long term, and due to the very low risk of Reye syndrome but much higher risk of death due to the SCDs even in children, aspirin should be added with an anti-inflammatory dose even in childhood into the acute and chronic phase treatments of the SCDs (43).

ACS is a significant cause of mortality in the SCDs (44). It occurs most often as a single episode, and a past history is associated with a higher mortality rate (44). Similarly, all of 14 patients with ACS had just a single episode, and two of them were fatal in spite of the immediate RBCs and ventilation supports and antibiotic therapy in the present study. The remaining 12 patients are still alive without a recurrence at the end of the 10-year follow up period. ACS is the most common between two to four years of age, and its incidence decreases with aging (45). As a difference from atherosclerotic consequences, the incidence of ACS did not show an increase with aging in the present study, and the mean ages of the patients with ACS and SCDs were similar (30.3 vs 30.5 years, $p>0.05$, respectively). The decreased incidence with aging may be due to the high mortality rate during the first episode and/or an acquired immunity against various antigens, and/or decreased strength of immune response by aging. Probably, ACS shows an inborn severity of the SCDs, and the incidence of ACS is higher in severe patients such as patients with the SCA and higher WBCs counts (44, 45). According to our long term experiences on the SCDs, the increased metabolic rate during infections accelerates sickling, thrombocytosis, leukocytosis, and capillary endothelial damage and edema, and terminates with end-organ failures-induced sudden deaths. ACS may also be a collapse of the pulmonary vasculature during such infections, and the exaggerated immune response against the sickled or just hardened RBCs-induced diffuse capillary endothelial damage may be important in the high mortality rate. A preliminary result from the Multi-Institutional Study of Hydroxyurea in the SCDs indicating a significant reduction of episodes of ACS with hydroxyurea therapy suggests that a considerable number of episodes are exaggerated with the increased numbers of WBCs and PLTs (46). Similarly, we strongly recommend hydroxyurea for all patients that may also be the cause of low incidence of ACS in our follow up cases (2.7% in males and 3.7% in females). Additionally, ACS did not show an infectious etiology in 66% (44, 45), and 12 of 27 cases with ACS had evidence of fat embolism in the other study (47). Beside that some authors indicated that antibiotics did not shorten the clinical course (48). RBCs support must be given as earliest as possible. RBCs support has the obvious benefits of decreasing sickle cell concentration directly, and suppressing bone marrow for the production of abnormal RBCs and excessive WBCs and PLTs. So they prevent further sickling-induced exaggerated capillary endothelial edema, disseminated tissue hypoxia, and end-organ failures-induced sudden deaths in the SCDs.

PHT is a condition of increased BPs within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of 25 mmHg or higher. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with PHT (49). The cause is often unknown. The underlying mechanism typically involves inflammation, fibrosis, and subsequent remodelling of the arteries. According to World Health Organization (WHO), there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with unknown mechanisms (50). PHT affects about 1% of the world population, and its prevalence may reach 10% above the age of 65 years (51). Onset is typically seen between 20 and 60 years of age (50). The most common causes are CHD and COPD (50, 52). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (53). But the pulmonary vascular remodeling in the COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone (53). In fact, all layers of the vessel wall appear to be involved with

prominent intimal changes (53). The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (53). On the other hand, PHT is also a common consequence, and its prevalence was detected between 20% and 40% in the SCDs (54, 55). Whereas we detected the ratio as 12.2% in the present study. The relatively younger mean ages of the study cases (30.8 years of males and 30.3 years of females) may be the cause of the lower prevalence of PHT in the present study. Although the higher prevalences of smoking and alcohol-like atherosclerotic risk factors in male gender, and although the higher prevalences of disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, COPD, and stroke-like atherosclerotic consequences in male gender, and the male gender alone is being a risk factor for the systemic atherosclerosis, the similar prevalences of PHT and ACS in both genders also support nonatherosclerotic backgrounds of them in the SCDs in the present study. Similar to our result, women have up to four times of the risk of men for development of idiopathic PHT, and generally develop symptoms 10 years earlier than men in the literature with the unknown reasons, yet (56). Although COPD and CHD are the most common causes of PHT in the society (52, 57), and although COPD (25.2% vs 7.0%, $p<0.001$) and CHD (18.0% vs 13.2%, $p<0.05$) were higher in male gender in the present study, PHT was not higher in males, again. In another definition, PHT may have a sickled or just hardened RBCs-induced chronic thromboembolic whereas ACS may have an acute thromboembolic backgrounds in the SCDs (58, 59), because the mean age of ACS was lower than PHT (30.3 and 34.0 years, $p<0.05$) in the present study, but its mortality was much higher than PHT in the literature (44, 45, 50).

COPD is the third leading cause of death with various underlying etiologies all over the world (60, 61). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, smoking, alcohol, male gender, excess weight, chronic inflammations, prolonged infections, and cancers may be the major underlying causes. Beside smoking, regular alcohol consumption is also an important risk factor for the pulmonary and systemic atherosclerotic processes, since COPD was one of the most common diagnoses in alcohol dependence (62). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (63). Probably an accelerated atherosclerotic process is the main structural background of functional changes seen with the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced fibrosis, atherosclerosis, and pulmonary losses. COPD may just be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body in COPD (64, 65). For example, there may be close relationships between COPD, CHD, PAD, and stroke (66), and CHD was the most common cause of deaths in the COPD in a multi-center study of 5.887 smokers (67). When the hospitalizations were researched, the most common causes were the cardiovascular diseases, again (67). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD (68). Similarly, COPD may just be the pulmonary consequence of the systemic atherosclerotic process caused by the sickled or just hardened RBCs in the SCDs (60).

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (69). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (70). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with the pulmonary, cardiac, renal, or hepatic diseases or smoking which are characterized by chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs which affect each other's functions in a short period of time. Similarly, digital clubbing is also common in the SCDs, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillaries in the SCDs. Beside the effects of SCDs, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% vs 6.6%, $p<0.001$) may also show some additional risks of male gender in the systemic atherosclerosis.

Leg ulcers are seen in 10% to 20% of the SCDs, and the ratio was 13.5% in the present study (71). Its prevalence increases with aging, male gender, and SCA (72). Similarly, its ratio was higher in males (19.8% vs 7.0%, $p<0.001$), and mean age of the leg ulcer patients was higher than the remaining ones in the present study (35.3 vs 29.8 years, $p<0.000$). The leg ulcers have an intractable nature, and around 97% of them relapse in a period of one year (71). As an evidence of their atherosclerotic background, the leg ulcers occur in the distal segments of the body with a lesser collateral blood supply (71). The sickled or just hardened RBCs-induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillaries may be the major causes, again (72). Prolonged exposure to the sickled or just hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCDs. The sickled or just hardened RBCs-induced venous insufficiencies may also accelerate the highly destructive process by pooling of causative bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, pooling of blood may be the main cause of delayed wound and fracture healings in the lower

extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the leg ulcers in males. Although presence of a continuous damage of hardened RBCs on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBCs counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBCs counts may decrease severity of pain and tissue damage (32). Because the main action of hydroxyurea may be the suppression of hyperproliferative WBCs and PLTs in the SCDs (31), prolonged resolution of leg ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBCs and PLTs counts-induced exaggerated capillary endothelial inflammation and edema.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being, and increased prevalence of excess weight all over the world. For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it became the most common cause of chronic liver disease even at childhood, nowadays (73). NAFLD is a marker of pathological fat deposition combined with a low-grade inflammation which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (73). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalences of cardiovascular diseases (74). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (75). NAFLD may be considered as one of the hepatic consequences of the metabolic syndrome and SCDs (76). Probably smoking also takes role in the inflammatory process of the capillary endothelium in liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (77). Increased oxidative stress, inactivation of antiproteases, and release of proinflammatory mediators may terminate with the systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol is much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites there. Chronic infectious or inflammatory processes and cancers may also terminate with an accelerated atherosclerosis in whole body (78). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (78, 79). As a result, cirrhosis may also be another atherosclerotic consequence of the SCDs.

The increased frequency of CRD can also be explained by aging of the human being, and increased prevalence of excess weight all over the world (80, 81). Aging, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, inflammatory or infectious processes, and cancers may be the main underlying causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged endothelial cells of the renal arteriols. Due to the continuous irritation of the vascular endothelial cells, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis, tissue hypoxia, and infarcts. Excess weight-induced hyperglycemia, dyslipidemia, elevated BPs, and insulin resistance may cause tissue inflammation and immune cell activation (82). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BPs ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (81). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BPs with excess weight (83). Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (83). However, along with the increased BPs, these changes cause a hemodynamic burden on the kidneys in long term that causes chronic endothelial damage (84). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much faster (83). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (85). Although some authors reported that alcohol was not related with the CRD (85), various metabolites of alcohol circulate even in the renal capillaries, and give harm to the renal capillary endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis in the renal vasculature (78). Although CRD is due to the atherosclerotic process of the renal vasculature, there are close relationships between CRD and other atherosclerotic consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (86), and the most common cause of death was the cardiovascular diseases in the CRD again (87). The sickled or just hardened RBCs-induced capillary endothelial damage may be the main cause of CRD in the SCDs, again (88).

CHD is the most common of the cardiovascular diseases (89). In adults who go to the emergency department with an unclear cause of pain, about 30% have pain due to CHD (90). Although half of cases are linked to genetics, physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, high BP, high blood glucose, dyslipidemia, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be the most common causes (91). It is the reduction of blood flow to the heart muscle due to build-up of atherosclerotic plaques secondary to the chronic inflammation of the arteries. It can present with stable angina, unstable angina, myocardial infarction, and sudden cardiac death (89). It is usually symptomatic with

increased basal metabolic rate and emotional stress (92). It is the cause of deaths in 15.6% of all deaths, globally (92). So it is the most common cause of death in the world, nowadays (92). In the United States in 2010, about 20% of those over the age of 65 years had CHD, while it was present in 7% of those between the ages of 45 to 64 years, and 1.3% of those between 18 and 45 years of age, and the rates were higher among men (93). On average, women experience symptoms 10 years later than men, and women are less likely to recognize symptoms and seek treatment (91). Women who are free of stress from work life show an increase in the diameter of their blood vessels, leading to decreased progression of atherosclerosis (94). Similarly, CHD was detected as 18.0% vs 13.2% in men and women in the present study respectively ($p<0.05$).

Stroke is an important cause of death, and usually develops as an acute thromboembolic event on the chronic atherosclerotic background. Aging, male gender, smoking, alcohol, and excess weight may be the major underlying causes. Stroke is a common complication of the SCDs, too (95, 96). We detected prevalences of stroke as 12.1% vs 7.5% in males and females in the present study, respectively ($p<0.05$). Similar to the leg ulcers, stroke is particularly higher with the SCA and higher WBCs counts (97). Sickling-induced capillary endothelial damage, activations of WBCs, PLTs, and coagulation system, and hemolysis may cause inborn and severe capillary endothelial inflammation, edema, and fibrosis in the SCDs (98). Probably, stroke may not have a macrovascular origin in the SCDs, and diffuse capillary endothelial edema may be much more important (99). Infections, inflammations, medical or surgical emergencies, and emotional stress may precipitate stroke by increasing basal metabolic rate, sickling, and capillary endothelial edema. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of cases is developed secondary to the increased WBCs and PLTs-induced exaggerated capillary endothelial inflammation and edema in the absence of prominent fibrosis, yet (46).

The venous capillary endothelium may also be involved in the SCDs (100). Normally, leg muscles pump veins against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When the leaflets are damaged, varices and telangiectasias develop. DVT may also cause varicose veins and telangiectasias. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus physical examination must be performed in the upright position. Although the relatively younger mean ages and significantly lower body mass index of the SCDs cases in the literature (10), the prevalences of DVT and/or varices and/or telangiectasias of the lower limbs were relatively higher in the present study (9.0% vs 6.6% in males and females, $p>0.05$, respectively), indicating an additional venous involvement of the SCDs. Similarly, priapism is the painful erection of penis that can not return to its flaccid state within four hours in the absence of any stimulation (101). It is an emergency because repeated damaging of the blood vessels may terminate with fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (101). It is mainly seen with SCDs, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (102, 103). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types (104). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood can not return adequately from the penis as in the SCDs, and they are very painful (101, 104). RBCs support is the treatment of choice in acute whereas hydroxyurea should be the treatment of choice in chronic phases (105). According to our experiences, hydroxyurea is highly effective for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillaries if initiated later in life.

Warfarin is an anticoagulant, and first came into large-scale commercial use in 1948 as a rat poison. It was formally approved as a medication to treat blood clots in human being by the U.S. Food and Drug Administration in 1954. In 1955, warfarin's reputation as a safe and acceptable treatment was bolstred when President Dwight David Eisenhower was treated with warfarin following a massive and highly publicized heart attack. Eisenhower's treatment kickstarted a transformation in medicine whereby CHD, arterial plaques, and ischemic strokes were treated and protected against by using anticoagulants such as warfarin. Warfarin is found in the List of Essential Medicines of WHO. In 2020, it was the 58th most commonly prescribed medication in the United States. It does not reduce blood viscosity but inhibits blood coagulation. Warfarin is used to decrease the tendency for thrombosis, and it can prevent formation of future blood clots and reduce the risk of embolism. Warfarin is the best suited for anticoagulation in areas of slowly running blood such as in veins and the pooled blood behind artificial and natural valves, and in blood pooled in dysfunctional cardiac atria. It is commonly used to prevent blood clots in the circulatory system such as DVT and pulmonary embolism, and to protect against stroke in people who have atrial fibrillation (AF), valvular heart disease, or artificial heart valves. Less commonly, it is used following ST-segment elevation myocardial infarction and orthopedic surgery. The warfarin initiation regimens are simple, safe, and suitable to be used in ambulatory and in patient settings (106). Warfarin should be initiated with a 5 mg dose, or 2 to 4 mg in the very elderly. In the protocol of low-dose warfarin, the target INR value is between 2.0 and 2.5, whereas in the protocol of standard-dose warfarin, the target INR value is between 2.5 and 3.5 (107). When warfarin is used and international normalised ratio (INR) is in therapeutic range, simple discontinuation of the drug for five days is usually enough to reverse the effect, and causes INR to drop below 1.5 (108). Its effects can be reversed with phytomenadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate, rapidly. Blood products should not be

routinely used to reverse warfarin overdose, when vitamin K1 could work alone. Warfarin decreases blood clotting by blocking vitamin K epoxide reductase, an ezyme that reactivates vitamin K1. Without sufficient active vitamin K1, clotting factors II, VII, IX, and X have decreased clotting ability. The anticlotting protein C and protein S are also inhibited, but to a lesser degree. A few days are required for full effect to occur, and these effects can last for up to five days. The consensus agrees that patient self-testing and patient self-management are effective methods of monitoring oral anticoagulation therapy, providing outcomes at least as good as, and possibly better than, those achieved with an anticoagulation clinic. Currently available self-testing/self-management devices give INR results that are comparable with those obtained in laboratory testing. The only common side effect of warfarin is hemorrhage. The risk of severe bleeding is low with a yearly rate of 1-3% (109). All types of bleeding may occur, but the most severe ones are those involving the brain and spinal cord (109). The risk is particularly increased once the INR exceeds 4.5 (109). The risk of bleeding is increased further when warfarin is combined with antiplatelet drugs such as clopidogrel or aspirin (110). But thirteen publications from 11 cohorts including more than 48.500 total patients with more than 11.600 warfarin users were included in the meta-analysis (111). In patients with AF and non-end-stage CRD, warfarin resulted in a lower risk of ischemic stroke (p= 0.004) and mortality (p<0.00001), but had no effect on major bleeding (p>0.05) (111). Similarly, warfarin resumption is associated with significant reductions in ischemic stroke even in patients with warfarin-associated intracranial hemorrhage (ICH) (112). Death occured in 18.7% of patients who resumed warfarin and 32.3% who did not resume warfarin (p= 0.009) (112). Ischemic stroke occured in 3.5% of patients who resumed warfarin and 7.0% of patients who did not resume warfarin (p= 0.002) (112). Whereas recurrent ICH occured in 6.7% of patients who resumed warfarin and 7.7% of patients who did not resume warfarin without any significant difference in between (p>0.05) (112). On the other hand, patients with cerebral venous thrombosis (CVT) those were anticoagulated either with warfarin or dabigatran had low risk of recurrent venous thrombotic events (VTEs), and the risk of bleeding was similar in both regimens, suggesting that both warfarin and dabigatran are safe and effective for preventing recurrent VTEs in patients with CVT (113). Additionally, an INR value of about 1.5 achieved with an average daily dose of 4.6 mg warfarin, has resulted in no increase in the number of men ever reporting minor bleeding episodes, although rectal bleeding occurs more frequently in those men who report this symptom (114). Non-rheumatic AF increases the risk of stroke, presumably from atrial thromboemboli, and long-term low-dose warfarin therapy is highly effective and safe in preventing stroke in such patients (115). There were just two strokes in the warfarin group (0.41% per year) as compared with 13 strokes in the control group (2.98% per year) with a reduction of 86% in the risk of stroke (p= 0.0022) (115). The mortality was markedly lower in the warfarin group, too (p= 0.005) (115). The warfarin group had a higher rate of minor hemorrhage (38 vs 21 patients) but the frequency of bleedings that required hospitalization or transfusion was the same in both group (p>0.05) (115). Additionally, very-low-dose warfarin was a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer (116). The warfarin dose was 1 mg daily for 6 weeks, and was adjusted to maintain the INR value of 1.3 to 1.9 (116). The average daily dose was 2.6 mg, and the mean INR was 1.5 (116). On the other hand, new oral anticoagulants had a favourable risk-benefit profile with significant reductions in stroke, ICH, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding (117). Interestingly, rivaroxaban and low dose apixaban were associated with increased risks of all cause mortality compared with warfarin (118). The mortality rate was 4.1% per year in the warfarin group, as compared with 3.7% per year with 110 mg of dabigatran and 3.6% per year with 150 mg of dabigatran (p>0.05 for both) in patients with AF in another study (119). On the other hand, infections, medical or surgical emergencies, or emotional stress-induced increased basal metabolic rate accelerates sickling, and an exaggerated capillary endothelial edema-induced myocardial infarction or stroke may cause sudden deaths in the SCDs. So lifelong aspirin with an anti-inflammatory dose plus low-dose warfarin may be a life-saving treatment regimen even at childhood both to decrease severity of capillary endothelial inflammation and to prevent thromboembolic complications in the SCDs (120).

The spleen is found in all vertebrates with a similar structure to the lymph nodes. It acts primarily as a blood filter, and removes old and abnormal RBCs and recycles the iron. Additionally, it synthesizes antibodies and removes antibody-coated bacteria and blood cells from the circulation. Like the thymus, the spleen has only efferent lymphatic vessels, and it is the major lymphatic organ of the body. It has a central role in the reticuloendothelial system, and retains the ability to produce lymphocytes after birth. The spleen acts as a pool of peripheral blood cells which are released in case of a need. For example, it stores half of the body's monocytes in mice (121). In case of an injury, the monocytes migrate to the injured tissues and transform into dendritic cells and macrophages, and assist tissue healing (122). It was detected in the present study that 56.2% of cases of the first and 45.6% of cases of the second groups (p<0.05) had autosplenectomy, and these ratios were the highest ones among all other affected tissues of the body. So the spleen is probably the primarily affected organ in the SCDs, and it may act as a chronic inflammatory focus, particularly due to the high WBCs content (123). Although, a 28-year follow-up study of 740 veterans of World War II with surgical removal of spleen on the battlefield found that they showed significant excesses of mortality from pneumonia and CHD (124), the prevalence of CHD was lower in females with the higher prevalence of autosplenectomy in the present study.

As a conclusion, the hardened RBCs-induced capillary endothelial damage initiates at birth, and terminates with multiorgan failures even at childhood. Parallel to digital clubbing, all of the atherosclerotic risk factors or consequences including smoking, alcohol, disseminated teeth losses, COPD, ileus, cirrhosis, leg ulcers, CHD, CRD, and stroke were higher, and autosplenectomy and mean age of mortality were lower in males which can not be explained by effects of smoking and alcohol alone at the relatively younger mean age. So autosplenectomy may be a good whereas male gender alone may be a bad prognostic factor, and digital clubbing may have an atherosclerotic background in the SCDs.

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# BARRIERS AND FACILITATORS OF PALLIATIVE CARE FOR ADULT HEART FAILURE PATIENTS: INTEGRATIVE REVIEW

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## Abstract

Introduction: Heart failure (HF) patients usually experience symptoms such as dyspnea, tiredness, cognitive impairment, and pain. Those symptoms contribute to a decline in physical functioning and a limitation in their ability to do their daily tasks. Palliative care (PC) is crucial for people with HF because it focuses on improving the quality of life and can reduce symptoms and improve function. Qatar aims to introduce PC services for adult patients with HF.

Objective: This integrative review aims to investigate the barriers, facilitators, and the outcomes to the provision of palliative care among adult patients with HF.

Methods: Whittemore and Knafl's framework guided this integrative review. Using three databases, twenty (n=20) peer-reviewed articles, published between 2011 and 2022, were included in the integrative review. The Mixed Methods Appraisal Tool was used to assess the quality of these articles. The data was then extracted and thematically analyzed before being synthesized.

Results: The barriers, facilitators, and outcomes of providing PC services to individuals with HF were identified from the perspectives of patients, healthcare providers, and healthcare organizations.

Conclusion: Gaining a comprehensive understanding of these barriers, facilitators, and outcomes associated with providing PC services to adults with HF is central for the effective implementation of such services for this patient population in Qatar.

Keywords: heart failure, palliative care, barriers, facilitators

## Barriers and Facilitators of Palliative Care for Adult Heart Failure Patients: Integrative Review

Cardiovascular disease, particularly heart failure (HF), is a leading cause of death worldwide (Singh et al., 2021). It results from physiological and functional abnormalities in the myocardium that lead to impaired ventricular filling and ejection of blood (Inamdar & Inamdar, 2016). Several risk factors are related to HF, including coronary artery disease (CAD), heart valve disease, high blood pressure, diabetes, smoking, and obesity (Mayo-Clinic, 2023). Patients with advanced HF usually experience symptoms such as dyspnea, tiredness, cognitive impairment, and pain (Ziehm et al., 2016b). These symptoms contribute to a decline in physical functioning and a restriction in daily activities. Furthermore, patients with advanced HF suffer from a range of psychosocial, socioeconomic, and emotional burdens including increased depression and job loss, in addition to devastating functional impairment that can have an impact on their overall quality of life (Caraballo et al., 2019).

Therefore, given the high symptom load and low survival rates, palliative care (PC) is crucial for people with HF because it focuses on quality of life, reduces symptoms, and improves function (Singh et al., 2021).

According to the World Health Organization (WHO), PC "an approach that improves the quality of life of patients and their families facing the problems associated with life threatening illness, through the prevention and relief of suffering" (Ivany & While 2013, p. 441). PC has been recommended for patients with HF to reduce symptoms, improve quality of life, avoid hospitalizations, and potentially avoid visits to the emergency room (Singh et al., 2021). However, McIlvenna and Allen (2016) identified several barriers to PC in HF. These authors indicated that HF patients underused PC treatments compared to cancer patients. In Qatar, cancer PC services are well developed compared to those for HF. Plans are being developed to launch PC services for these patient populations (Ministry of Public Health, n.d.).

As a result, the purpose of this integrative review is to investigate the barriers and facilitators to providing PC to adult patients with HF. It is hoped that understanding such barriers and facilitators will inform the implementation of PC for adult patients with HF in Qatar.

## Background

HF is a complex clinical disease in which the heart is unable to sustain sufficient cardiac output to fulfill metabolic needs (Malik et al., 2022). HF is caused by any condition that inhibits ventricular filling or ejection of blood into the systemic circulation (Malik et al., 2022). As a result, HF patients experience tiredness and dyspnea as well as decreased exercise tolerance and fluid retention (Malik et al., 2022).

## The Prevalence and Incidence Rates of HF

Globally, 64.3 million individuals live with HF (Groenewegen et al., 2020). The prevalence rate of recognized HF patients varies across different nations. For example, the prevalence of HF in the United States was 2.4% in 2012, and it is expected to grow to 3.0% by 2030 (Savarese et al., 2022). In Norway, researchers found that overall HF prevalence increased from 1.98% in 2013 to 2.42% in 2016 (Savarese et al., 2022). In India, the prevalence rate of HF ranged from 1.3 to 4.6 million people (Savarese et al., 2022). The prevalence rate in other Asian countries was estimated to be 2% to 3% in Hong Kong, 5% in Indonesia, 1% to 2% in the Philippines, 0.6% in South Korea, and 6% in Japan (Savarese et al., 2022). Savarese et al. (2022) stated that the prevalence of data on the rate of HF in the Middle East was limited, but the estimated range is from 1.3% to 6.7%. Furthermore, there is no reported prevalence rate of HF patients in Qatar. Generally, in Qatar, the mortality rate from cardiovascular diseases from 2011- 2013 was 8.3 per 100,000 Qatari males and 4.1 per 100,000 non-Qatari males aged 20 -44 years (Ministry of Public Health, 2020).

## Pathophysiology and Treatment of Heart Failure

Clinically, HF is divided into two basic categories based on the heart's functional status: heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF; Inamdar & Inamdar, 2016). Understanding the pathophysiology of HFpEF and HFrEF assists in the selection of therapy targets (Schwinger, 2021). HFpEF is characterized by anatomical and cellular changes that prevent the left ventricle from adequately relaxing (Schwinger, 2021). HFrEF, on the other hand, is defined by significant cardiomyocyte loss, either acute or chronic, resulting in systolic failure (Schwinger, 2021).

Coronary heart disease, hypertension, diabetes mellitus, obesity, chronic lung disorders, inflammation or chronic infection, metabolic diseases, and treatment with cardiotoxic drugs are the main risk factors for HF (Schwinger, 2021). According to Schwinger (2021) shortness of breath, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, tiredness, weakness, and lethargy are all symptoms of HF. Kaasalainen et al. (2011) reported the following frequencies of distressing symptoms; HF fatigue (42% to 82%), dyspnea (18% to 88%), pain (20% to 78%), insomnia (36% to 48%), anxiety (2% to 49%), constipation (12% to 42%), anorexia (11% to 43%), edema (33% to 44%), and depression (6% to 59%).

There are various ways to classify HF. One is according to the severity of the functional status of the individuals using the New York Heart Association (NYHA) classification system (Mayo Clinic, 2023). The NYHA classifies HF into four classes. The classes include Class I, where the patient has no symptoms of HF; Class II, where the patient can perform daily tasks; Class III, where the patient experiences difficulties performing daily tasks;

and Class IV, where the patient exhibits severe symptoms even when at rest. In general, patients with HF who fall into NYHA classes III or IV are referred to PC, with HF symptoms palliation being the top priority (Asano et al., 2019). Bierle et al. (2021) stated that "the unpredictable but overall, progressively declining illness trajectory of patients with HF makes palliative care ideal because it does not depend on the prognosis and can be integrated into all phases of the patient's treatment and disease" (p. 9). Furthermore, HF is classified as acute or chronic based on the time of onset (Inamdar & Inamdar, 2016).

The objective of HF treatment is to enhance symptom management and quality of life while decreasing hospitalizations (Malik, 2022). According to McCuistion et al. (2020), vasodilators, angiotensin-converting enzyme inhibitors (ACE), diuretics, and some betablockers are among the pharmacological agents used to treat HF. Vasodilators lower venous blood return, which lowers cardiac filling; ACE inhibitors dilate venules and arterioles and lower blood volume; diuretics lower blood volume; and beta-blockers lower the effect of the sympathetic nervous system, which lowers heart rate and blood pressure (McCuistion et al., 2020). Non-pharmacological measures are also used to treat HF. These include dietary and lifestyle changes such as reduced salt intake and fluid intake, and smoking cessation (McCuistion et al., 2020).

## Palliative Care for Heart Failure

The National Consensus Project Clinical Practice Guidelines for Quality Palliative Care (NCP guidelines) defines palliative care (PC) as "an interdisciplinary care delivery system designed to anticipate, prevent, and manage severe illness to optimize the quality of life for patients, their families, and caregivers" (Kim et al., 2022, p. 151). PC aims to lessen all types of suffering, including physical, psychological, and spiritual pain, by addressing advanced care planning, symptom alleviation, and caregiver or family support (Sullivan & Kirkpatrick, 2020). The word "palliative" is derived from the Greek word pallium, which refers to a cloak-like garment that the Greeks wore outside of their regular working lives and which they saw as a source of protection. English speakers changed the succeeding Latin word palliatus to become "palliate" in the fifteenth century. In figurative usage, the term was changed from referring to one's cloak to a means of protection and reducing the severity of harm or disease (Sullivan & Kirkpatrick, 2020). The PC movement was first established at St. Christopher's Hospice in the UK in 1967 (Sullivan & Kirkpatrick, 2020). In the 1980s, the first hospital-based palliative care was founded, and the first palliative medicine program began in the USA in 1987 (Sullivan & Kirkpatrick, 2020). Sullivan and Kirkpatrick (2020) stated that palliative medicine received approval from the Accreditation Commission in 2004. Hospice and palliative medicine were approved as recognized specialties by the American Board of Medical Specialties in 2006, (Sullivan & Kirkpatrick, 2020). In addition, McIlvennan and Allen (2016) reported that even though the terms "hospice" and "palliative care" are frequently used interchangeably, they have distinct meanings. PC is a word used to refer to all types of care that, without regard to the prognosis, prioritize symptom control and quality of life over curative therapy ( McIlvennan & Allen, 2016). The authors explained that for those suffering a life-limiting disease or injury, hospice is often regarded as a division of PC. Hospice care is a type of PC delivery mechanism intended for people nearing the end of their lives ( McIlvennan & Allen, 2016). PC can be classified into primary, secondary, and tertiary McIlvennan & Allen, 2016). Primary PC refers to the basic skills and information that all healthcare providers must possess to address the common palliative needs of cardiac patients ( Mallvennan & Allen, 2016). Secondary palliative care is usually provided by palliative care experts ( McIlvennan & Allen, 2016). Tertiary PC is delivered in academic healthcare settings where scholars research, practice, and teach complex PC issues (McIlvennan & Allen, 2016).

## Domains of Palliative Care

Effective PC for HF patients must comprise holistic assessment and monitoring (Westlake & Smith, 2015). The domains of PC are physical, social, psychological, spiritual, cultural, transitions to hospice, and ethical/legal (DeGroot et al., 2020). The physical domain is focused on physical performance enhancement, whereas the social domain is concerned with the screening of various types of social support and resources (DeGroot et al., 2020). The psychological domain includes the evaluation of mental health as well as the stress and coping mechanisms of patients and their family caregivers (DeGroot et al., 2020). The spiritual realm is concerned with the assessment and facilitation of the spiritual activities of the patients and their family caregivers (DeGroot et al., 2020). The cultural domain assesses, and respects values, beliefs, and traditions linked to health, disease, family caregiver obligations, and decision-making (DeGroot et al., 2020). Within the realm of transition to hospice care, healthcare providers examine, recognize, and manage the signs and symptoms of impending death, while the domain of ethics addresses any relevant ethical decision making (DeGroot et al., 2020).

## Barriers to Palliative Care Services

There are various barriers to PC: patient and their family caregivers related, health care providers related, and organizational related barriers (Romano, 2020). Perrin and Kazanowski (2015) reported that among barriers for the patients and their family caregivers in critical care units was the misunderstanding about PC. The authors explained further that the most common misperception was that PC was just for people who are dying. Moreover, Ufere et al. (2019) reported the barriers to PC at the healthcare provider and organizational levels. At the healthcare provider level, the authors highlighted how the culture of the healthcare providers influenced PC perception in their practice (Ufere et al., 2019). Moreover, at the organizational level, Ufere et al. (2019) explained

that insufficient funding, lack of time spent delivering PC, and insufficient acknowledgment of the relevance of PC by health organizations was found to be a barrier to PC utilization.

## Impact of Palliative Care

The purpose of PC efforts is to improve the quality of life for persons suffering from severe conditions such as HF and their informal caregivers, such as family members (Grant & Graven, 2020). Bekelman et al. (2011) reported that HF patients and their family caregivers valued the early implementation of PC services, particularly psychological and symptom management. Hospitals with policies and practices in place to promote PC delivery had higher patient outcomes (Grant & Graven, 2020). Overall, PC improves patient satisfaction, autonomy in end-of-life care, symptom burden, quality of life, and reduces the use of other healthcare services (Romano, 2020).

## The Context in Qatar

The Qatar National Health Strategy 2018–2022, was unveiled by the MOPH, and it intends to improve the health of residents in Qatar (MOPH, n.d). The improvement of the health of persons with chronic diseases through integrated and accessible services is one of the strategy's seven top pillars. The Qatar National Health Strategy indicates that individuals with chronic diseases require the information and skills to effectively manage their conditions and avoid needless hospitalization and emergency room visits. This will help these individuals with chronic illnesses attain autonomous and healthy lives. HF is a chronic disease that needs regular cardiac care. The Heart Hospital (HH) in Qatar is a specialty center with a total of 116 beds specifically for individuals with cardiovascular disease including HF (Hamad General Hospital, n.d). Currently, the HH strategy aims to introduce PC services for adult patients with HF.

## Aim

The introduction of PC services for adult patients with HF in Qatar will allow better services to this patient population. Therefore, an integrative review was conducted to understand the barriers and facilitators of the provisions of PC among adult patients with HF. This understanding will help to develop strategies to implement PC for adult patients with HF in Qatar.

## Methodology

This project follows the integrative review framework developed by Whittemore and Knafl (2005). An integrative review was chosen as the most appropriate method to investigate the barriers and facilitators to the provision of PC among adult patients with HF. An integrated review synthesizes previous empirical or theoretical material to provide more thorough knowledge of a specific phenomenon or healthcare problem (Whittemore & Knafl, 2005). Whittemore and Knafl (2005) explained that integrative review permits the inclusion of different sources of literature and has the potential to contribute to the creation of evidence-based nursing practice. This framework has five stages, which are problem identification, literature search, data evaluation, data analysis, and synthesis of the findings.

## Problem Identification

Whittemore and Knafl (2005) stated that clear identification of the problem is the first step of the integrative review framework. The Qatar National Health Strategy 2018–2022 indicates that individuals with chronic diseases require the information and skills to effectively manage their conditions and avoid needless hospitalization and emergency room visits. There is a need to introduce PC services for adult patients with HF in Qatar.

Furthermore, the HH strategic plan aims to introduce a PC service to provide better services to this patient population. Therefore, this integrative literature review aims to identify the barriers and facilitators of the provision of PC for adult HF patients. It is expected this integrative literature review will facilitate the implementation of PC services in Qatar for adult patients with HF.

## Literature Search

The search for literature in this integrative review was done with assistance from a librarian at the University of Calgary in Qatar. Searches were conducted in the following databases: Cumulative Index to Nursing and Allied Health Literature (CINAHL), MEDLINE, and Embase. The key search terms were heart failure, cardiac failure or chronic heart failure or congestive heart failure, palliative care or end of life care or terminal care, barriers, obstacles or challenges or difficulties, facilitators, or enablers. The Boolean operators AND and OR were utilized to combine or extend the search. The search limiters were peer-reviewed articles, articles published in English, and articles published from 2011 to 2022. After applying these limiters, 836 articles were identified.

## Data Evaluation

The identified 836 articles were evaluated for inclusion in this integrative review. Two hundred and seventy-six duplicate articles were removed, bringing the total to 560 articles.

The titles and abstracts of the 560 articles were reviewed, and 465 articles were found to be irrelevant and were removed. A full text review was conducted for the remaining 95 articles using the inclusion and exclusion criteria (see Table 1). The inclusion criteria were (a) primary studies; (b) studies that focused on adult heart failure; (c) studies related to hospital based palliative care; and (d) studies focused on the barriers and facilitators of the provision of palliative care for HF. The exclusion criteria were (a) posters, reviews, opinions, and conference abstracts;

**Table 1: Inclusion and Exclusion Criteria**

| Inclusion | Exclusion |
|---|---|
| Primary studies | Literature Reviews, reports, opinions, conference abstracts |
| Palliative care for adult with heart failure | Articles focused on palliative care for pediatric with heart failure |
| Studies related to hospital based palliative care | Studies focused on community based palliative care |
| Studies focused on the barriers and facilitators of the provision of palliative care for HF | Studies focused on barriers, facilitators of palliative care of other diseases |
| Peer-reviewed studies | Secondary sources such as literature reviews |
| Studies published from 2011 to 2022 | Studies published before 2011 |
| Studies in full text and written in English | Non-English language studies |

(b) articles focused on pediatric heart failure; (c) studies focused on community palliative care services; and (d) articles focused on palliative care of other diseases. Based on the inclusion and exclusion criteria, 76 articles were eliminated. Therefore, 19 primary articles remained for further consideration. One article was added following a manual search bringing the total to 20 articles (see Figure 1). The summary of the screening process is presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart (see Figure 1).

To assess the methodological quality of the retrieved articles for this integrative review, the Mixed Methods Appraisal Tool (MMAT) version 2018 was employed (Hong et al., 2018). The MMAT assesses the methodological quality of different research designs, such as qualitative studies, quantitative descriptive studies, quantitative randomized controlled trials, quantitative non-randomized studies, and mixed methods studies (Hong et al., 2018). The MMAT was developed in 2006 and was revised in 2018 (Hong et al., 2018). According to Hong et al. (2018), the quality of the research should be assessed by two independent reviewers. The MMAT contains two key parts for evaluating the research study's quality. For both parts of the screening procedure, possible replies are (a) yes, (b) no, and (c) cannot tell (Hong et al., 2018). Part one begins with two screening questions asking about: (a) the presence of a clear research question, and (b) the data collection that addresses the research question. The studies are then evaluated in the second part using specific criteria for the study design.

There were 14 qualitative studies, two quantitative descriptive studies, two quantitative non-randomized studies, one mixed method research, and one study that collected both qualitative and quantitative descriptive data. The 14 qualitative studies were evaluated based on the following: (a) they used an appropriate approach to answer the research question; (b) the data collection methods were adequate; (c) the findings were derived from the data; (d) the findings were validated by the data; and (e) there was consistency between the data sources, data collection, analysis, and interpretations. The two quantitative descriptive studies were evaluated based on the following: (a) relevant sampling strategy was used to answer research question; (b) the sample represents the target population; (c) appropriate measurements were used; (c) the risk of non-response bias was low; and (d) appropriate statistical measurement were used to answer the research question. The quantitative non-randomized studies were evaluated based on the following: (a) the participants represent the target population; (b) using appropriate measurement for the outcome; (c) there were complete outcome data; (d) the confounders were accounted for the design and analysis; and (e) during the study period, the intervention was administered as intended. The mixed method studies were evaluated for their quantitative and qualitative properties in addition to the following: (a) there was an adequate rationale for using a mixed methods design to address the research question; (b) the different components of the study were effectively integrated to answer the research question; (c) the outputs of the integration of qualitative and quantitative components were adequately interpreted; (d) divergences and inconsistencies between quantitative and qualitative results adequately addressed; and (e) the different components of the study adhere to the quality criteria of each tradition of the methods involved. The one study that used both qualitative and quantitative descriptive data collection was evaluated based on both descriptive quantitative and quantitative MMAT criteria. The overall quality of the chosen studies was found to be adequate, so they were all included for further analysis.

## Data Analysis

Data analysis phase requires that data be sorted, coded, categorized, and summarized into a cohesive and integrated conclusion regarding the research topic (Whittemore & Knafl, 2005). Data analysis entails the following steps: data reduction, data display, data comparison, conclusion drawing, and verification (Whittemore & Knafl, 2005).

**Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PR**

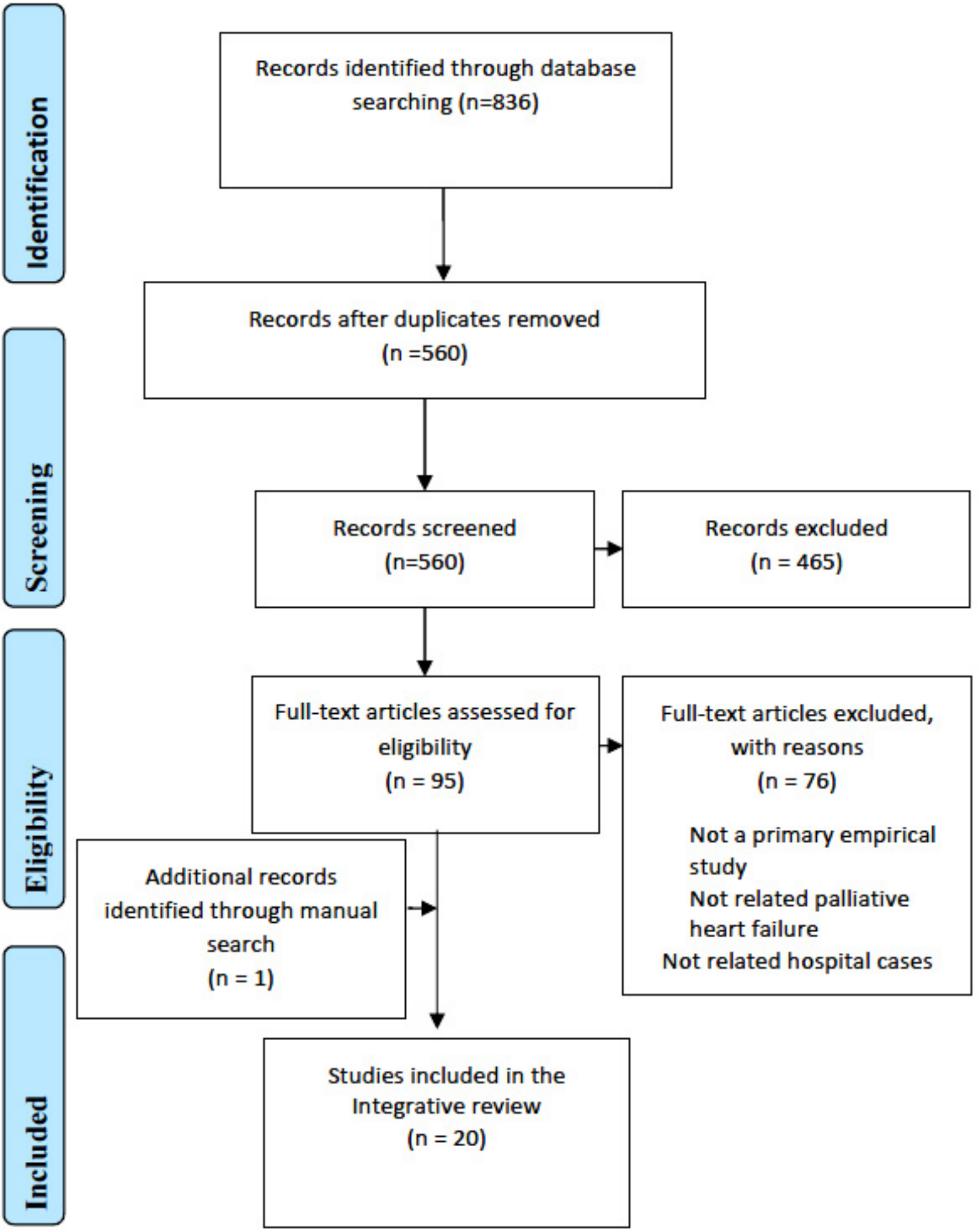
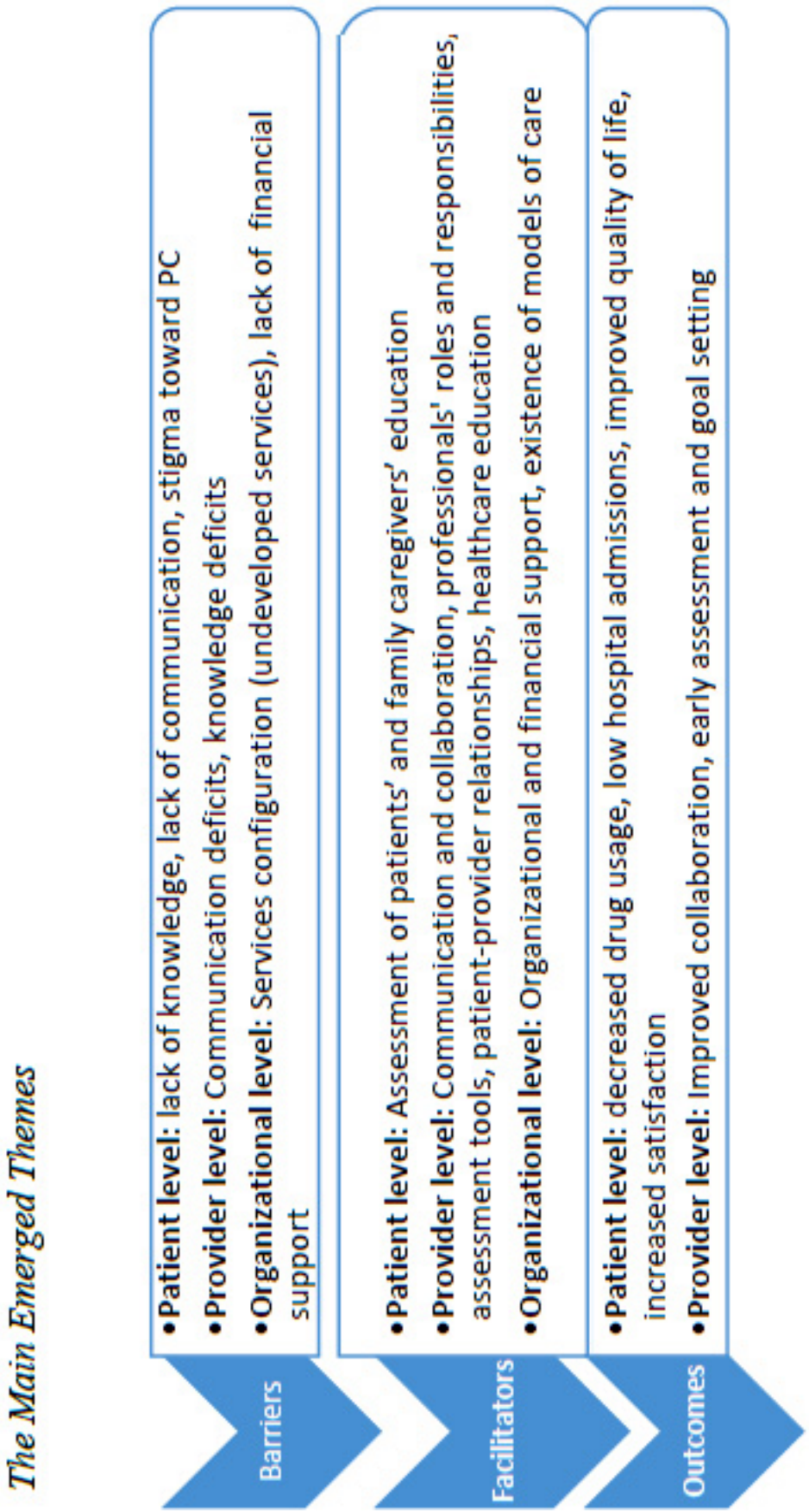


**Figure 2: The Main Emerged Themes**



In the data reduction phase, data is abstracted and compared to categorize and group relevant data. The extracted data from the selected articles was displayed in a matrix table to identify common themes. In the data display step, the extracted information was summarized to capture essential information in a succinct and focused way (Whittemore & Knafl, 2005).

The data was categorized by author, research purpose, study design, sample size and characteristics, data collection instruments, and context of where it was obtained. After reviewing the summary data extraction sheets, two reviewers agreed on identifying significant and relevant components for each phase. The differences and similarities amongst the data abstracted from the studies were then examined, followed by a synthesis of findings.

The data comparison phase entails an iterative process of evaluating data presentations of primary source data to uncover patterns, themes, or correlations (Whittemore & Knafl, 2005). Consequently, three themes emerged that provided answers to the research question raised in this review: What are the barriers and facilitators, and the outcomes in the provision of palliative care for adult patients with HF? The final phase of the data analysis is the conclusion drawing and verification, which shifts the interpretative effort from the description of patterns and correlations to higher levels of abstraction. In this phase, several revisions by two reviewers were carried out during the data verification process to assure the integrity of the reported findings. Figure 2 presents a diagram representing the barriers, the facilitators, and the outcomes that were obtained from the 20 articles.

## Barriers

### Patients and Family Caregiver Barriers

Barriers identified at the patient and family caregiver level were lack of knowledge, stigma regarding PC, and lack of communication related to PC. A Lack of knowledge was reported related to the nature of the disease (Ziehm et al., 2016a; Ziehm et al., 2016b), as well as unfamiliarity and misunderstanding of the diagnosis and its consequences (Browne et al., 2014). Four studies reported a lack of knowledge of PC as a model of care (Hadler et al., 2020; Metzger et al., 2013; Shibata et al., 2022; Ziehm et al., 2016b). For example, In Metzger et al.'s (2013) study, patients had no or little prior knowledge of the phrase "palliative care" and were unaware of the existence of the PC services. Additionally, Hadler et al. (2020), reported that patients mentioned prior familiarity with PC but wrongly confused it with hospice. In two studies, the patients and their families frequently believed that PC was only significant in the latter stages of life (Metzger et al., 2013; Shibata et al., 2022). In Ziehm et al.'s (2016a) study, patients reported a lack of information about the substance and structure of PC services. In addition, a lack of knowledge about therapies, such as devices and medications, was also reported as a barrier to PC management (Browne et al., 2014; You et al., 2017). In Browne et al.'s (2014) study, patients and caregivers reported a lack of knowledge about the adverse effects of medications. While in You et al.'s (2017) study, patients and their family caregivers reported a lack of knowledge regarding the limitations or possible risks of life-sustaining therapies. The stigma surrounding PC was a considerable barrier to its use. Four studies reported that the patients and their family caregivers linked PC with death and PC was on an equal footing with euthanasia (Singh et al., 2021; Siouta et al., 2018; Ziehm et al., 2016a; Ziehm et al., 2016b). Therefore, patients and their family caregivers avoided discussions related to PC. Additionally, other communication barriers with health care providers were reported by the patients and their family caregivers (Browne et al., 2014; You et al., 2017).

According to You et al. (2017), patients and their families wanted reliable information regarding the prognosis; yet emotional distress or anxiety about the nature of advanced HF prevented them from engaging in dialogues about PC provision. While in Browne et al.'s (2014) study, patients reported that cognitive impairment, comorbidities, and prognostic worry contributed to the deterioration of PC conversations.

### Healthcare Provider Barriers

Barriers identified at the healthcare provider level were communication and knowledge deficits. A communication deficit regarding the start and management of PC for patients with HF was reported by healthcare providers as a barrier. Three studies stated that discussing prognosis was difficult due to the disorder's complex and unpredictable nature (Ecarnot et al., 2018; Glogowska et al., 2016; Siouta et al., 2018). Additionally, healthcare providers stated that they avoided discussing end-of-life issues whenever possible and frequently cited lack of time as an excuse (Ament et al., 2022; Browne et al., 2014; Ecarnot et al., 2018; Siouta et al., 2018). Moreover, healthcare providers reported variations in the approaches used to treat HF within healthcare specialties that caused communication discrepancies (Ecarnot et al., 2018; Singh et al., 2021; Ziehm et al., 2016b). In the study of Ecarnot et al. (2018) it was reported that practices varied among different health and paramedical professionals. Singh et al. (2021) and Ziehm et al. (2016b) stated that multiple team members were caring for the patient with differing beliefs about care, which complicated the communication about when to refer the patient to PC services. Additionally, in two studies, the nurses reported a lack of support in their workplace to participate in PC related communication (Singh et al., 2021; You et al., 2017). In the study of You et al. (2017), nurses felt neither challenged nor supported in their communication. While Singh et al. (2021) reported that healthcare providers emphasized their lack of communication skills as limiting the patient's access to PC.

A lack of knowledge about PC was reported as a barrier. A lack of knowledge has been reported about HF and its unpredictable prognosis in several studies (Bonares et al., 2021; Glogowska et al., 2016; Green et al., 2011; Kavalreratos et al., 2016; Lewin et al., 2017; Ziehm et al.,

2016a; Ziehm et al., 2016b). Other studies reported a lack of understanding of PC and described the perception that PC only helps cancer patients (Green et al., 2011; Ziehm et al., 2016a; Ziehm et al., 2016b).

### Healthcare Organization Barriers

Barriers identified at the healthcare organization level were service configuration and a lack of financial support for PC services. Three studies reported on the service configuration of PC as a barrier (Browne et al., 2014; Singh et al., 2021; Szekendi et al., 2016). Browne et al. (2014) reported that inadequate PC services configuration, such as unclear pathways, inadequate coordination, and unprepared services led to unplanned admissions of patients to emergency departments. While in the study of Szekendi et al. (2016), it was reported that there was no common explanation of PC services within the organizations which led to limiting PC referrals. Similarly, Singh et al (2021) reported that the PC service often has limited resources with few team members covering the hospital. Another obstacle reported was the lack of financial support for PC services (Ziehm et al., 2016b). Ziehm et al. (2016b) reported that PC healthcare providers were underpaid, which led to an inadequate number of PC professionals providing such services.

## Facilitators

### Patient and Family Caregiver Facilitators

The facilitator identified at the patient's and family caregiver level was the patient and caregivers' education. One study reported that the major criterion for discussing the prognosis and probable transfer to PC was believed to be the assessment of patient's education needs related to disease progression and the provision of PC (Green et al., 2011). Three studies reported the importance of patient education about PC as a concept (Hjelmfors et al., 2018; Ziehm et al., 2016a; Ziehm et al., 2016b). It was further explained in the Ziehm et al. (2016a), and Ziehm et al. (2016b) studies that educating patients about PC led to increased quality of life and dispelled the myth that PC is only suitable for cancer patient care. Hjelmfors et al. (2018) reported that a question prompt list (QPL) was used successfully to educate and facilitate communication between patients and their families on the course of their HF and their end-of-life care. Additionally, two studies reported that educating patients and their family caregivers about advance care planning was a key enabler of participation in PC (Glogowska et al., 2016; You et al., 2017). You et al. (2017) reported that advanced care planning was an important procedure that helped with in-hospital goals-of care conversations about PC, while in Glogowska et al. 's (2016) study, it was acknowledged that advanced care planning helped the patients to decide whether to die at home or in the hospitals.

### Healthcare Provider Facilitators

Communication and collaboration between different healthcare providers, recognition of the professionals' roles and responsibilities, tools to identify PC needs, patient-provider relationships, and PC-related health care education were identified as facilitators at the healthcare provider level. Five studies reported communication among healthcare team members as a facilitator (Ecarnot et al., 2018; Metzger et al., 2013; Siouta et al., 2018; Ziehm et al., 2016a; Ziehm et al., 2016b). Greater collaboration among different clinical disciplines, according to those studies, improved PC access for HF patients. Furthermore, clarification of healthcare providers' roles and responsibilities facilitated discussions and management of end-of-life care in PC (Ament et al., 2022; Glogowska et al., 2016; Green et al., 2011; Hjelmfors et al., 2022; Szekendi et al., 2016; You et al., 2017). Four studies found that HF nurses and general practice nurses played a more important role for PC needs assessment among this patient population (Ament et al., 2022 Glogowska et al., 2016; Green et al., 2011; You et al., 2017). Moreover, Hjelmforse et al. (2022) reported that physicians oversaw delivering prognostic information, while nurses assisted in initiating discussions related to PC. In the study of Szekendi et al. (2017), it was reported that PC teams were seen as experts in complex symptom management and goal-of-care discussions. Conducting structured PC needs assessment was identified as an important facilitator towards determining and discussing the need for PC. Examples of tools used for this purpose were the HF question prompt list (HF-QPL) (Hjelmfors et al., 2022), the prognosis disease tool (PC-NAT), supportive PC indicator tool (SPCIT) (Hadler et al., 2020), identification of patients with heart failure with palliative care need (I-HARP) (Ament et al., 2022 ), and algorithms tool (Singh et al., 2021; Siouta et al., 2018; You et al., 2017; Ziehm et al., 2016a).

The literature indicated that these tools were not just only useful in identifying the needs of the HF patients (Ament et al., 2022; Singh et al., 2021; Siouta et al., 2018; Ziehm et al., 2016a), but also served as a guide in the dialogue and assisted the patients and their family caregivers in asking key questions about HF disease progression and PC provision (Hadler et al., 2020; Hjelmfors et al., 2022; You et al., 2017).

Having a good relationship between patients and their healthcare provider facilitated the discussions of the goal of care and enhanced their access to PC services (Ament et al., 2022; Glogowska et al., 2016; Green et al., 2011; Hadler et al., 2020; Hjelmfors et al., 2022; Kavalerator et al., 2016; Siouta et al., 2018; Singh et al., 2021). Five studies reported that close relationships between the patients and their healthcare providers led to a better understanding of what the patient's PC needs were (Ament et al., 2022; Glogowska et al., 2016; Green et al., 2011; Hjelmfors et al., 2022; Siouta., 2018). Other studies reported that the patients' relationships with their healthcare practitioners improved their access to PC services (Hadler et al., 2022;

Kavalerator et al., 2016; Singh et al., 2021). Educating healthcare providers about PC has been reported as a facilitator of PC (Ament et al., 2022; Green et al., 2011; Kavalerator et al., 2016; Shibata et al., 2022; Singh et al., 2021; Ziehm et al., 2016a). Five studies found that PC education significantly increased healthcare providers' knowledge and abilities in addressing the PC needs for HF patients (Ament et al., 2022; Green et al., 2011; Shibata et al., 2022; Singh et al., 2021; Ziehm et al., 2016a). Kavalerator et al.'s (2016) study reported that networking and peer education about PC has led to greater and earlier referrals to PC services.

### Healthcare Organizations Facilitators

Organizational and financial support and the development of a PC model of care were identified as facilitators at the level of healthcare organizations. Healthcare organizations' support for healthcare providers was reported as a facilitator for PC (Ament et al., 2022; Hjelmfors et al., 2022; Szekendi et al., 2016; You et al., 2017; Ziehm et al., 2016a). Two studies reported that organizational guidelines and practices, such as availability of time and spaces, fostered a more inter-professional approach to goal-of-care conversations about PC needs (Hjelmfors et al., 2022; You et al., 2017). Ament et al. (2022) reported that organizational e-health advancements in the setting of HF enhanced the early identification of palliative care needs for patients with HF. The authors further explained that using e-health information and assessments of PC needs improved patients' empowerment and participation in goal-of-care conversations. Moreover, Szekendi et al. (2016) reported that the hospital management support enhanced the visibility and Implementation of PC services programs. Similarly, Ziehm et al. (2016a) reported that PC units served as advisers for other experts' specializations. The authors underlined in their study that incorporating PC services within hospitals or care units allowed patients to stay in the same units while receiving PC. Financial and organizational support and the development of models of care were reported as additional facilitators for PC services. In Ament et al.'s (2022) study, it was reported that financial motivation helped the implementation and sustainability of change.

An additional facilitator was the development of models of care for PC (Green et al., 2011; Singh et al., 2021). Green et al. (2011) reported that comprehensive models, such as chronic illness prognosis models, enhanced the physicians' insight and clinical judgment about their patients with HF. While Singh et al. (2021) reported that improvements to the organization's HF-PC model allowed for more access to PC services. The authors explained further that a multidisciplinary care team model for patients with HF should be comprised of the cardiologists, HF nurses, PC nurses, PC physicians, pharmacists, physiotherapists, and social workers.

## Outcomes of Palliative Care

### Patient and Family Caregiver Outcomes

Outcomes identified at the patients' and family caregivers' level were decreased medication usage, a lowered rate of hospital admissions, improved quality of life, and increased satisfaction with PC healthcare providers. Two studies reported reduced medication usage, such as opioid medications, because the treatment of pain had improved (Ziehm et al., 2016a; Ziehm et al., 2016b). Furthermore, literature reports a reduced hospitalization rate as an outcome of PC services (Hadler et al., 2020; Lewin et al., 2016; Siouta et al., 2018; Ziehm et al., 2016a). Three studies reported that integrating PC into the HF treatment plan lowered readmission rates and hospitalization (Hadler et al., 2020; Siout et al., 2018; Ziehm et al., 2016a). Lewin et al.'s (2016) study reported that at baseline, there were no differences in emergency room (ER) visits ($p = 0.92$); however, following the PC intervention, the group who received PC had substantially fewer ER visits than the control group who did not receive PC intervention ($p = 0.067$).

In addition, quality of life improvement was reported as an outcome of PC services in five studies (Cheang et al., 2015; Hadler et al., 2020; Siouta et al., 2018; Ziehm et al., 2016a; Ziehm et al., 2016b). Those studies reported that PC services improved the quality of life of patients with HF by reducing and preventing physical and psychological pain. Furthermore, three studies reported increased satisfaction with PC healthcare providers as an outcome of PC (Lewin et al., 2017; Metzger et al., 2013; Ziehm et al., 2016b). In Lewin et al.'s (2017) study, patients and their family caregivers reported that the ability to receive continuous care across institutions helped to establish their trust with the PC team and the HF team. Similarly, in Metzger et al.'s (2013) study, patients' and their family caregivers described PC clinicians as listening, being more sympathetic, taking more time, and having a holistic emphasis. In Ziehm et al.'s (2016b) study, it was reported that the patients and their family caregiver's satisfaction with PC healthcare professionals was high and PC management was seen as useful support for efficient coping.

### Healthcare Provider Outcomes

Improved collaboration among disciplines, as well as early assessment and goal setting by healthcare providers, were among the outcomes identified at the healthcare provider level. Three studies reported that collaboration improvement was an outcome of PC services (Cheang et al., 2015; Lewin et al., 2017; Siouta et al., 2018). Cheang et al. (2015) reported significant interdisciplinary collaboration between different PC and HF healthcare team members. In Lewin et al.'s (2017) study, it was reported that the program's integrated approach enabled increased communication between the HF and PC teams. Comparably, Siouta et al. (2018) reported that integrating PC required combining the administration and clinical disciplines to achieve patient-centered care.

In addition, two articles reported that early assessment and goal-of-care establishment were outcomes of PC services (Ament et al., 2022; Metzger et al., 2013). Early examination and goals-of-care discussions, according to Metzger et al. (2013), resulted in agreement with the clinician's prognosis, and the patient expressed changes in their objectives throughout time based on a shared perspective of the prognosis with the PC physicians. In comparison, Ament et al.'s (2022) study found that assessing patient needs and goals-of-care on time Resulted in better patient outcomes.

## Discussion

The purpose of this integrative review was to identify the barriers, the facilitators, and the outcomes of the provision of PC for adult patients with HF. The findings in this review successfully characterized the barriers that needed to be overcome and identified elements that will facilitate the provision of PC in Qatar. This review also identified potential positive outcomes that can be assessed following the implementation of PC. As a result, this understanding would help to develop strategies to implement PC for adult patients with HF in Qatar.

### Barriers of Palliative Care

The patient and caregivers, healthcare providers, and healthcare organizations have their own specific barriers that contributed to the lack of utilization of PC for patients with HF. This review showed that the lack of knowledge related to PC was associated with insufficient communication with healthcare providers, which was manifested in the reporting stigma about PC. Comparable findings have been reported in the literature. According to Abu-Odah et al. (2020), inadequate knowledge about PC and stigma toward PC by families and caregivers were significant personal barriers to the provision of PC for cancer patients.

Additionally, Lalani and Cai (2022) stated that fear, values, and beliefs about end of life caused patients and families to have an unclear understanding of PC and to be unwilling to accept such treatment for a family member suffering from a severe illness. This review further indicated that patients with HF should be educated on the course and consequences of their disease as early as possible so that they may communicate their wishes and treatment choices to their healthcare provider. Moreover, renaming PC to "Supportive Care" might have a good influence on patients, resulting in better patient outcomes and eliminating PC misconception (Bonares et al., 2021).

Healthcare providers acknowledged that PC was required for patients with HF. Yet, the biggest barriers for healthcare providers were unclear communication structures and a lack of knowledge about the content and importance of PC. The review highlighted that inadequate knowledge about PC was identified as a barrier that led to a lack of communication among the various professional groups involved in the care of patients with HF. Similar findings have been reported in the literature. Lalani and Cai (2022) stated that clinicians indicated a variety of concerns about the lack of a clear definition and regulation of PC services, which resulted in confusion, misunderstanding, and delays in providing adequate PC services for patients with cancer. This misunderstanding led to challenges in communication between healthcare providers and made referrals of cancer patients to PC services difficult. Moreover, Iyer et al. (2020) explained that PC professionals expressed concerns about not understanding the PC strategy, not having early communication on end-of-life choices, and an unclear disease trajectory for patients with chronic obstructive pulmonary disease.

Despite the great need for PC provision for patients with HF, this integrative review indicated that health care organizations still lack the service configuration and the needed funding to support PC. This review indicated that several healthcare providers acknowledged the limited

**Table 2: The Main Themes and Sub-Themes**

| | Barriers | Facilitators | Facilitators |
|---|---|---|---|
| Patient and family caregiver | Lack of knowledge, lack of communication, stigma toward PC | Assessment of patients' and family caregivers' education | Decreased drug usage, low hospital admissions.<br>Improved quality of life, increased satisfaction |
| Healthcare providers | Communication deficits, knowledge deficits | Communication and collaboration, professionals' roles, and responsibilities., assessment tools, patient-provider relationships, healthcare education | Improved collaboration, early assessment, and goal setting |
| Healthcare organizations | Services configuration, lack of financial support | Organizational and financial support, existence of models of Care | |

resources provided for the PC service, particularly staff shortages. This caused clinicians to be cautious when deciding whether to refer a patient to a PC. These findings are supported by the results of other studies that investigated PC among other patient populations. For example, Abu-Odah et al. (2020) reported that the primary barriers to providing PC for cancer patients were limited staffing and limited physical infrastructure such as facilities, equipment, supplies, beds, and chairs. The authors explained that the most significant impediment to providing PC for cancer patients was a lack of financial support for PC services. Additionally, Lalani and Cai (2022) claimed that funds should be made available to improve PC resources and foster the development of PC services for cancer patients.

### Facilitators of Palliative Care

The patient and their family caregiver, the healthcare provider, and healthcare organizations all had their own specific facilitators that contributed to the improvement in the utilization of PC for patients with HF. Overall, providing PC for patients with HF was supported and facilitated when education was provided to patients and their family caregivers. The review explained that educating patients about PC improved their quality of life and eliminated the idea that PC was only appropriate for cancer patients. It was further suggested in this review that tools such as QPL assisted patients and family caregivers during clinical consultations and enabled them to ask appropriate questions regarding the HF trajectory and end-of-life care. Evidence from other contexts presented comparable results. Bennardi et al. (2020) reported that educating patients improved awareness of PC benefits and support of PC usage through exposure to clear end-of-life information. These benefits were connected to greater PC utilization among cancer patients (Bennardi et al., 2020). Additionally, Halabi and Bani (2022) stated that providing information that improves the understanding of PC services improved the recovery of patients after a stroke.

For healthcare providers, the key facilitators of delivering PC for patients with HF were communication, clearly defined responsibilities, and roles, using appropriate tools to assess PC needs, and education. This review showed that understanding the professional roles and their obligations in communicating illness prognosis and end-of-life care is vital to consider. This is because the HF healthcare providers have a variety of specialties, education, and experiences. These findings were echoed in other literature. Albers et al. (2016) explained that cooperation and shared educational activities between the PC team and geriatric medicine led to a comprehensive and holistic approach that improved the quality of life of those suffering from significant chronic dementia. Moreover, Bennardi et al. (2020) stated that collaboration and exchanging educational meetings between oncologists and the PC team, as well as participation in multidisciplinary meetings, increased cancer patients' utilization of PC services during the negotiation phase with patients and their family caregivers.

The development of PC delivery models, along with proper organizational and financial support, allowed healthcare organizations to deliver PC more easily to patients with HF. This review concluded that providing funding and resources enabled access to specialist PC for patients with HF, which improved their functions, symptoms, quality of life and reduced the number of hospitalizations. Such funding is important for educating and training healthcare providers to enhance their communication skills and encourage the exchange of information and skills between disciplines. Evidence from other contexts suggested similar findings. Iyer et al. (2020) evaluated the outcomes of investing in innovative PC delivery models such as telemedicine PC, increasing the number of trained pulmonary nurses in PC, and integrating PC specialists in clinics alongside pulmonary practitioners. The authors reported that nurse-led early PC models enhanced quality of life, mood, and survival in patients with advanced disease. Additionally, VanDoorne et al. (2022) claimed that the hospital's financial support aided in the development of care models and directed the planning of an annual PC conference for geriatric patients with chronic illnesses.

## Outcomes of Palliative Care

This review has shown that PC for patients with HF is related to positive outcomes including lowered drug consumption, lowered hospitalizations, improved quality of life, and enhanced trust between healthcare providers and patients. This review also revealed that one of the PC domains was psychological, which includes assessing mental health as well as the stress and coping mechanisms of patients and their family caregivers. As a result, the quality of life of patients with HF improved by reducing and preventing physical and psychological burdens. Furthermore, the review found that the ability to get continuous therapy across institutions improved patients' and family caregivers' communication and confidence in their PC team. PC physicians were described as listening more, being more empathetic, spending more time with patients, and having a holistic approach. Evidence from other contexts suggested similar findings. Patel et al. (2017) stated that PC consultation has been linked to higher patient satisfaction and decreased critical care unit admission in hospitalized patients with end stage liver disease. Additionally, Vanbutsele et al. (2020) stated that early integration of PC in cancer treatment improved quality of life toward the end of life. Improved collaboration among disciplines, as well as early assessment and goal setting were the outcomes of integrating PC into HF treatment at the healthcare provider level. In conclusion, this review indicated that the incorporation of PC services into HF therapy improved communication between the HF and PC teams. As a result, early examination and goal-of-care talks improved, and patient-centered care was achieved. Evidence from other contexts suggested similar findings. Evans et al. (2019) claimed that multidisciplinary discussions were successful with advanced cancer patients who would benefit from a palliative approach to care. Additionally, Zou et al. (2020) stated that early integrated PC delivered in a multidisciplinary collaborative

model improved management of dyspnea, increased participation in advanced care planning, and decreased hospitalization rates at the end-of-life for patients with chronic idiopathic pulmonary fibrosis. Furthermore, Zou et al. (2020) explained that models such as collaborative disciplines led to decreased hospital deaths, increased adherence to patient wishes for care and place of death, and enhanced patient and caregiver experiences.

### Strengths and Limitations

In this integrative review, significant barriers, and facilitators, as well as the outcomes of implementing PC for HF patients, were emphasized. However, comprehending the review's strengths and limitations is crucial. One notable strength is that this integrative review is the first of its kind to shed light on the barriers and facilitators of providing PC for HF patients in Qatar. Additionally, the incorporation of quantitative, qualitative, and mixed methods studies offered a more holistic and integrated understanding of the state of science and care delivery for this patient population. Furthermore, the review's methodology was another strength, as it followed a rigorous framework outlined by Whittemore and Knafl (2005), which relied on a thorough search strategy to identify relevant articles. The support of an experienced librarian also assisted in the search technique, while a two-researcher conducted the evidence selection method diligently. Furthermore, effective data synthesis of the results was accomplished using a standardized data extraction tool. It is also noteworthy that the results of this integrative review were derived from current, peer-reviewed, and original literature published within the last ten years.

However, the review had certain limitations that need to be reported. The search was restricted to articles published only in English, which may have excluded relevant data published in other languages. Additionally, none of the research reviewed was conducted in Qatar, or the neighbouring nations of the Arabian Gulf. Therefore, it is important to approach the generalizability of the results of this integrative review to Qatar or this region with caution.

### Implications and Recommendations

This integrative review has important implications for nursing practice. This review successfully highlighted the positive impact of PC treatments on adult patients with HF, emphasizing the need for a multidisciplinary approach involving PC clinicians, cardiac nurses, social workers, and physicians. The findings of this review can be utilized to support the creation of programs that facilitate effective team-based PC therapies. Enhanced communication skills and targeted education among multidisciplinary team members will improve healthcare professionals' understanding of PC-related issues, resulting in better PC delivery and a better quality of life for the patients. However, discussing death and dying openly is still not common practice in many cultures, and people often put off having these conversations even when they are getting close to the end of their lives because it is such a difficult subject. Therefore, promoting open discussion and education on death and dying at all levels is critical. These discussions will eliminate the stigma and promote a better understanding of the provision of PC among individuals with HF and their family members. Future research may focus on determining the unique barriers and facilitators to the provision of PC for individuals with HF in Qatar. The findings of this integrative review can provide a framework for researchers to follow.

## Conclusion

This integrative review provided a comprehensive understanding of the barriers, facilitators, and positive outcomes for the provision of PC among adult HF patients. Communication and knowledge deficits were identified as the main barriers for patients, family caregivers, and healthcare providers, whereas the lack of services configuration and financial support were barriers at the healthcare organization level. Key facilitators included patient and family education, communication, establishing professional roles and responsibilities, assessment tools, patient-providers relationship, providers education, PC care models, and financial assistance. PC services were associated with positive outcomes, including decreased drug use, hospital admission, and improved quality of life and satisfaction for patients. Healthcare providers also benefited from improved communication and early goal setting and assessment. These findings can be utilized to improve the implementation of PC services for this patient population through educational initiatives aimed at promoting understanding among healthcare providers, patients, and their family members.

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# GRIEF UNITES US

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While the bombing of Gaza and the resulting loss of civilians continues, I urge the international community to stop the war now, protect civilians (including health-care workers), lift the 16-year blockade on Gaza immediately, and allow international aid to enter Gaza to support the health-care system that has already collapsed.

I dedicate this simple article to the brave health workers in the Gaza strip. I share with you bereavement for doctors who devoted themselves to the patients and even more they gave their lives. I know you are comrades, brodies and fathers to those wounded and dying children, women and old men. I can see everyone of you hovering over sores and festering wounds, witnessing amputations, standing by vomit and diarrhea. When necessary you held and kiss the poor, poor children. I know for sure how your presence has saved many lives, that the magnetic flood of sympathy and friendship provide more benefits than all the medicine in the world. I know you loved die rank and file , their individual stories were death stories that mattered most, death stories that captured the essence of the war. Though you know words could never convey the experience in hospitals of the dying, could never convey multiple meanings in a wounded soldier's smile. The voices touches of thousands of children live inside you, their words and agonies all are yours .You will carry them to your graves and beyond. I know all because I am an Iraqi physician.

I just cannot see myself living like this anymore. I peek at the breaking news on my phone fearing the worst with each breaking news. I read headlines on the television screen and watch the collective punishment of Palestinians of the Gaza strip every minute with disappointment and slowly sinking to the floor. It is nearly two months and the huge toll of deaths among children ground us to a nub and it is still unclear whether there will be a ceasefire. But what is definitively gone is the hope that I clung to, that the crisis will slow down. By a cruel twist of fate the suffering of the civilians in Gaza is progressing shockingly fast. Civilians find themselves barely able to stay alive. They have to fight so hard to live only a version of life which is worse than death.

Moreover, the long-standing blockade of Gaza and repeated cycles of violence over the years have led to a critical nutritional crisis among Palestine refugees in Gaza, particularly affecting vulnerable groups, including children, women, and older people. Anaemia rates have become alarming despite preventive and curative measures. Even before the current conflict, Gaza was grappling with a dire need for mental health and psychosocial support services. In 2022, 26•4% of the population required such assistance, the highest among all areas of UNRWA operation.

Children have inherent rights, regardless of their race, ethnicity, religion, nationality, geography, or any other aspect of identity. Silence kills. History will judge us for how we respond today—and the world's children are watching.

Globally, armed conflict has been repeatedly shown to cause pervasive harm to children directly and indirectly, causing physical injury, a range of illnesses and infections, malnutrition, psychological distress, disability, and death. Conflict has even been shown to harm children living far from the areas where combat is taking place. Both direct and indirect exposure to conflict are associated with multiple forms of severe adversity, which in turn is known to cause altered stress physiology, altered development, multiple physical and psychological morbidities, and early mortality. In short, exposure to armed conflict greatly alters a child's life course. That is what happened to my people in Iraq, does anyone remember?

What is happening now reminds me about the American Bison tragedy because of the same brutal mentality leading the world. In 1860,an estimated 60 million bison roamed the American West. Two decades later the Bison population plunged to fewer than 300. Palestinians are not disposable, they are Human Beings and it is ironic that if the news came out that 7000 whales were killed the world would stand still!

When we entered the field of medicine, little did we know how prevalent grief would be, or the toll it can take- both professionally and personally. Medical education spends little time normalizing grief as part of practicing medicine. There are programs addressing suffering in all its dimensions for patients and patient's families, but not for physicians or other members of care teams.

Since the mass displacement and dispossession of Palestinians (also referred to as the Nakba) in 1948, health-care workers have been killed, and health-care facilities have been destroyed. Since October 7, 2023, Israeli military bombing of the Gaza Strip (or Gaza) has resulted in 73 health-care workers being killed, with 57

health-care facilities attacked as of Oct 24, 2023. Of these healthcare workers, 16 were killed while on duty. Some of the prominent healthcare workers who were killed include Omar Ferwana, former Dean of the Islamic University of Gaza School of Medicine, and Medhat Sedim, one of the very few board-certified plastic and burn surgeons in Gaza. Other health-care workers killed include nurses, paramedics, and others, many of whom were killed with their families while asleep at home. On Oct 17, 2023, the world witnessed the targeting of Al Ahli Arab hospital (the only Anglican mission hospital in Gaza and the oldest in Palestine) by a strike that is still under investigation. At that time, the hospital was partially operational, with patients, health-care workers, and hundreds of internally displaced civilians sheltering there.

The mounting losses and the unprocessed grief can contribute to emotional exhaustion and ultimately burnout.

Grief is the anguish experienced after significant loss (the loss of a loved one, a relationship, a self-image, or a dream) and in Palestine and many Middle East countries all the above!

This experience includes physiological distress, separation anxiety, confusion, yearning, obsessive dwelling on the past, and apprehension about the future.

Grief can manifest in multiple ways:
• Acute grief is defined as tearfulness, sadness, and insomnia as a response to loss, and typically lasts for less than a year,
• Anticipatory grief involves feelings of loss experienced prior to the expected loss.
• Complicated or prolonged grief manifests as intense and persistent grief that causes problems and interferes with daily life.
• Ambiguous grief refers to loss that does not allow for the possibility of closure (many of us experienced this during the pandemic).
• Disenfranchised grief involves a loss that is not openly acknowledged as legitimate by society and is often accompanied by feelings of shame, guilt, and further isolation (this can be a contributing factor to physician burnout).

Many of us are familiar with the five stages of grief — denial, anger, bargaining, depression, and acceptance — which psychiatrist Elisabeth Kübler-Ross introduced in 1969.

Her work marked a shift in how we communicated with patients nearing the end of their lives. In 2004, she and counselor David Kessler proposed that the five stages of grief can also apply to those who have lost a loved one, though the stages are not inherently linear nor all necessary for healthy grieving.

In 2019, Kessler suggested that moving beyond the five stages and finding meaning in our losses can be transformative.

Finally I quote what Hazel Grace said when August died in the novel titled The Fault in our stars by Gohn Green
*"and then I realized there was no one else to call, which was the saddest thing. The only person I really wanted to talk to about Augustus Water's death was Augustus Water." I realized then that funerals are not held for the dead, but for the living''*

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