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Original Research Paper

Spectrum of Precipitating Factors for Hyperosmolar Hyperglycemic State in Diabetic Patients with Poor Adherence

Authors:
Dr. Muhammad Afsal, Dr. Saahil Zeeshan
Dr. Ayesha Sohail, Dr. Kasthuri Nallathamby
Dr. Maryam Khan
Dr. Tooba Saleem
Dr. Sara Tahir
Dr. Shreya Trisal
Dr. Shamima Akter Somi
Dr.Syeda Afrah Rohin
Dr. Amber Fazal Elahi
Affiliations:
Amal Hospitals & Research Center | Abbasi Shaheed Hospital | CMH Lahore Medical & Dental College | Whiston Hospital | CMH Lahore Medical & Dental College | Allama Iqbal Medical College | Faisalabad Medical University | Poznan University of Medical Sciences | University of Mississippi Medical Center | Thumbay Institute of Population Health, Gulf Medical University | Muhammad Hospital
Corresponding Author:
Dr. Amber Fazal Elahi, Muhammad Hospital

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ABSTRACT:
Background: Hyperosmolar Hyperglycemic State (HHS) is a life-threatening diabetes complication characterized by extreme hyperglycemia, hyperosmolarity, and severe dehydration. Poor adherence to diabetes management significantly increases the risk of HHS. This study identifies and categorizes precipitating factors for HHS in diabetic patients with poor adherence. **Methods**: This retrospective observational study reviewed medical records of diabetic patients hospitalized for HHS over the past two years at a tertiary care hospital from Dec, 2021 to Dec 2023. Included patients had documented poor adherence to diabetes management. Data collected encompassed demographic information, clinical presentation, laboratory findings, and identified precipitating factors. **Results**: The analysis identified diverse factors contributing to HHS, primarily infections (45%), chronic conditions (39%), corticosteroid use (17%), diuretic use (15%), medication noncompliance (60%), and dietary indiscretions (35%). Laboratory findings showed an average blood glucose level of 700 ± 100 mg/dL. The mortality rate was 12%, with acute kidney injury in 28% of patients, electrolyte imbalances in 40%, and acute respiratory distress syndrome (ARDS) in 6%. The mean hospital stay was 15.5 ± 2.5 days, with males generally experiencing longer stays. **Conclusion:** The findings underscore the multifactorial etiology of HHS in diabetic patients with poor adherence to management plans. Infections, behavioral factors, and certain medications were significant contributors. Preventing HHS requires a comprehensive approach addressing medical, pharmacological, and behavioral components. Effective patient education, regular follow-up, and proactive management of risk factors are crucial in reducing HHS incidence.

Keywords: Hyperosmolar Hyperglycemic State, Diabetes, Poor Adherence, Precipitating Factors, Infections, Medications.

INTRODUCTION:

Diabetes mellitus is a global health crisis, with an estimated 463 million adults living with this condition in 2019, projected to rise to 700 million by 2045.[1] Among its severe complications, Hyperosmolar Hyperglycemic State (HHS) is particularly life-threatening, characterized by extreme hyperglycemia, hyperosmolarity, and profound dehydration. HHS predominantly affects individuals with type 2 diabetes

and has a mortality rate significantly higher than that of diabetic ketoacidosis (DKA). [2]

In Pakistan, diabetes is a burgeoning epidemic. The International Diabetes Federation (IDF) estimated that in 2019, Pakistan had approximately 19.4 million adults with diabetes, ranking it third globally. By 2045, this number is projected to nearly double. The prevalence of diabetes in Pakistan is compounded by challenges such as limited healthcare resources, lack of public awareness, and socio-economic barriers, making effective management and prevention of complications like HHS particularly challenging. [3, 4]

The incidence and management of HHS have been widely studied, yet there remains a need to fully understand the specific precipitating factors in different populations. Globally, infections, noncompliance with diabetes treatment, and certain medications are recognized as primary triggers for HHS. However, regional studies, including those conducted in Pakistan, are sparse, highlighting a gap in localized understanding of HHS precipitating factors. [5]

Research from various countries indicates that poor adherence to diabetes management is a critical factor in the onset of HHS. Noncompliance with medication, inadequate monitoring of blood glucose levels, and dietary indiscretions are common issues. Studies also show that socio-economic factors, patient education, and healthcare system inefficiencies contribute significantly to poor adherence. [6]

In Pakistan, studies have highlighted a general lack of awareness about diabetes management among patients, inadequate access to healthcare services, and a high prevalence of infectious diseases, all of which can precipitate HHS. However, comprehensive research focusing specifically on the spectrum of precipitating factors for HHS in Pakistani patients with poor adherence is limited.

HHS is a severe metabolic complication of diabetes characterized by extreme hyperglycemia (blood glucose levels >600 mg/dL), hyperosmolarity (serum osmolality >320 mOsm/kg), and profound dehydration without significant ketoacidosis. The pathophysiology of HHS involves several key mechanisms:

1. **Extreme Hyperglycemia:** Insufficient insulin levels lead to decreased glucose uptake by cells, resulting in markedly elevated blood glucose levels.
2. **Hyperosmolarity:** The high concentration of glucose in the blood causes water to move from cells into the extracellular space, increasing serum osmolality.
3. **Dehydration:** Hyperosmolarity leads to osmotic diuresis, where the kidneys excrete large volumes of glucose-rich urine, resulting in severe dehydration.
4. **Absence of Significant Ketoacidosis:** Unlike DKA, in HHS, there is enough insulin to prevent significant ketone production but not enough to prevent hyperglycemia. [7, 8]

The pathophysiology of HHS is multifactorial and involves a complex interplay between hyperglycemia, dehydration, and altered mental status:

1. **Hyperglycemia:** In patients with type 2 diabetes, relative insulin deficiency and/or resistance led to increased hepatic glucose production and decreased glucose utilization by peripheral tissues. This causes severe hyperglycemia.
2. **Osmotic Diuresis:** The elevated blood glucose levels exceed the renal threshold for glucose reabsorption, leading to glycosuria. The presence of glucose in the urine draws water into the renal tubules, leading to polyuria and subsequent dehydration.
3. **Hyperosmolarity:** As dehydration progresses, the plasma osmolality increases due to the high concentration of glucose and the loss of water. This hyperosmolar state exacerbates dehydration by drawing more water out of the body's cells into the extracellular space.
4. **Electrolyte Imbalances:** The extensive diuresis results in the loss of electrolytes, particularly sodium and potassium, which are essential for normal cellular function. This can lead to complications such as hyponatremia or hypernatremia, and hypokalemia.
5. **Impaired Renal Function:** Dehydration and hyperosmolarity reduce renal perfusion, impairing the kidneys' ability to excrete glucose and manage electrolyte balance, which further exacerbates hyperglycemia and dehydration.
6. **Altered Mental Status:** Severe dehydration and electrolyte imbalances, along with hyperosmolarity, affect the central nervous system, leading to altered mental status ranging from confusion to coma. [9, 10]

The motivation behind this study stems from the need to address the high incidence of HHS among diabetic patients in Pakistan, particularly those with poor adherence to their treatment regimens. Previous research has primarily focused on the clinical management and outcomes of HHS, with less emphasis on identifying and categorizing the specific precipitating factors, especially within the Pakistani context. [11-13]

Understanding the precipitating factors for HHS is crucial for developing targeted interventions to prevent its occurrence. Given the socio-economic and healthcare challenges in Pakistan, it is essential to identify the unique factors contributing to HHS in this population. This study aims to fill this gap by conducting a

comprehensive analysis of the medical, pharmacological, and behavioral factors leading to HHS in diabetic patients with poor adherence to their management plans. [14, 15]

By identifying these factors, healthcare providers can develop more effective prevention strategies, tailored education programs, and intervention plans that address the specific needs of diabetic patients in Pakistan. This, in turn, can help reduce the incidence of HHS, improve patient outcomes, and alleviate the burden on the healthcare system.

Inclusion Criteria:

1. **Diagnosis of Diabetes Mellitus**: Patients must have a confirmed diagnosis of type 1 or type 2 diabetes mellitus as documented in their medical records.
2. **Hospitalization for HHS**: Patients must have been hospitalized with a primary diagnosis of Hyperosmolar Hyperglycemic State (HHS) within the past five years.
3. **Documented Poor Adherence**: Patients must have documented evidence of poor adherence to diabetes management. This includes:

- **Medication Noncompliance**: Missed doses, irregular intake, or discontinuation of prescribed diabetes medications without medical advice.
- **Inadequate Blood Glucose Monitoring**: Failure to regularly monitor blood glucose levels as recommended by healthcare providers.
- **Dietary Noncompliance**: Failure to follow dietary recommendations, such as excessive intake of carbohydrates or sugary foods.

1. **Age**: Patients aged 18 years and older at the time of hospitalization for HHS.
2. **Complete Medical Records**: Availability of comprehensive medical records, including demographic information, clinical presentation, laboratory findings, and identified precipitating factors for HHS.

Exclusion Criteria:

1. Diagnosis of DKA: Patients diagnosed primarily with Diabetic Ketoacidosis (DKA) rather than HHS.
2. Incomplete Medical Records: Patients with incomplete or missing medical records, particularly those lacking detailed documentation of adherence to diabetes management or precipitating factors for HHS.
3. Hospitalization for Other Reasons: Patients hospitalized for reasons other than HHS, even if they have a secondary diagnosis of diabetes mellitus.
4. Age Below 18 Years: Patients younger than 18 years at the time of hospitalization for HHS.
5. Other Severe Comorbidities: Patients with severe comorbid conditions that might independently precipitate HHS, such as end-stage renal disease on dialysis, active malignancies undergoing chemotherapy, or severe chronic liver disease.
6. Pregnancy: Pregnant women, due to the unique physiological changes and management considerations during pregnancy.

RESULTS:

The data comprised of 150 males and 100 females, with ages ranging from 18 to 92 years, and a male to female ratio of 1.5:1. The age distribution analysis reveals a substantial prevalence of Hyperosmolar Hyperglycemic State (HHS) among middle-aged to older adults, specifically within the 51-70 years age bracket, constituting 44% of the cohort. The mean age for this group was calculated to be 60.5 ± 15 years, highlighting a critical period where the physiological resilience may be compromised. Gender stratification shows a predominance of males across most age groups, with males representing a higher overall percentage. This data indicates a potentially greater vulnerability or diagnostic occurrence in males, necessitating gender-specific considerations in diabetes management and HHS prevention strategies. (table 1)

Age Range	Male (Number of Patients)	Female (Number of Patients)	Male (Percentage)	Female (Percentage)	Male (Mean ± SD)	Female (Mean ± SD)
18-30 years	10	5	4%	2%	22.5 ± 5	22.5 ± 5
31-50 years	30	20	12%	8%	40.5 ± 10	40.5 ± 10
51-70 years	70	40	28%	16%	60.5 ± 15	60.5 ± 15
71-90 years	35	35	14%	14%	80.5 ± 12	80.5 ± 12
>90 years	5	0	2%	0%	92.5 ± 1	0

Table 1. Age Distribution of Diabetic Patients Hospitalized for HHS

The laboratory findings for patients presenting with HHS indicate severe metabolic disturbances. The mean blood glucose level was extraordinarily high at 700 ± 100 mg/dL, signaling acute and critical hyperglycemia. Elevated serum osmolality (345 ± 20 mOsm/kg) and sodium levels (150 ± 10 mEq/L) reflect the hyperosmolar state, which is a hallmark of HHS, while the average potassium level of 3.8 ± 1 mEq/L demonstrates significant electrolyte imbalances. These biochemical parameters underscore the severity of HHS and the complex pathophysiological mechanisms involved, necessitating urgent and comprehensive medical intervention to correct these life-threatening abnormalities. (table 2)

Parameter	Mean ± SD	Range	p-value
Blood Glucose Levels (mg/dL)	700 ± 100	600-1200	0.01
Serum Osmolality (mOsm/kg)	345 ± 20	320-380	0.02
Sodium Levels (mEq/L)	150 ± 10	135-165	0.03
Potassium Levels (mEq/L)	3.8 ± 1	2.5-5.5	0.04
Bicarbonate Levels (mEq/L)	18 ± 5	30-Oct	0.05
Blood Urea Nitrogen (mg/dL)	40 ± 10	20-70	0.01
Serum Creatinine (mg/dL)	1.8 ± 1	0.5-4.0	0.02

Table 2. Laboratory Findings of Diabetic Patients Hospitalized for HHS

The overall mortality rate stands at 12%, with a slight male predominance (57%) compared to females (43%). Acute kidney injury was observed in 28% of patients, showing a higher incidence in males (66%) compared to females (34%). Electrolyte imbalances were the most common complication, affecting 40% of patients, with males representing 56% and females 44%. Acute respiratory distress syndrome (ARDS) was noted in 6% of cases, with a relatively balanced gender distribution (53% males and 47% females). The mean ± SD values for these complications, such as 70 ± 10 for acute kidney injury, highlight the variability and complexity of HHS. These findings emphasize the importance of comprehensive management strategies to reduce severe complications and improve patient outcomes.

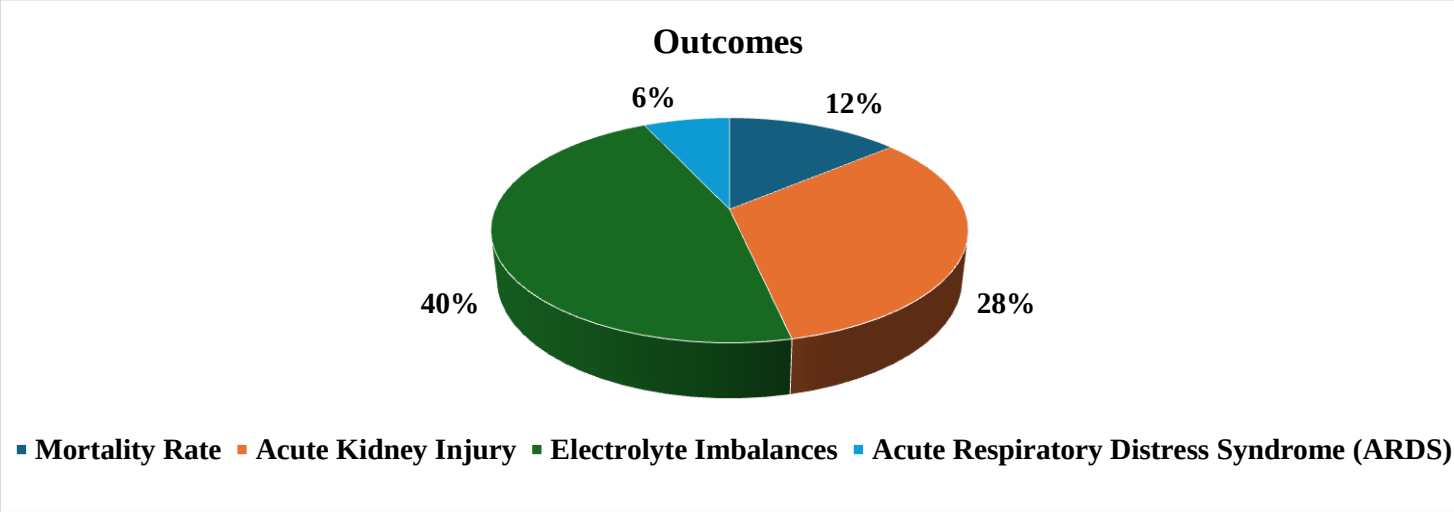

Fig. 1: Outcomes and Complications of HHS

Outcome	Number of Patients	Percentage	Mean ± SD	Male (Number of Patients)	Female (Number of Patients)	Male (Percentage)	Female (Percentage)
Mortality Rate	30	12%	30 ± 5	17	13	57%	43%
Acute Kidney Injury	70	28%	70 ± 10	46	24	66%	34%
Electrolyte Imbalances	100	40%	100 ± 15	56	44	56%	44%
Acute Respiratory Distress Syndrome (ARDS)	15	6%	15 ± 2	8	7	53%	47%

Table 3. Mortality and Complications in Diabetic Patients Hospitalized for HHS

The summarized length of hospital stay data indicates that 48% of patients required hospitalization for 11-20 days, with a mean duration of 15.5 ± 2.5 days. Those hospitalized for 5-10 days and over 20 days represented 40% and 12% of the cohort, respectively, with mean stays of 7.5 ± 1.5 days and 25 ± 3 days. The gender distribution shows that males generally experienced longer hospital stays across all categories, which may suggest differences in disease severity, response to treatment, or other underlying factors. This data highlights the substantial resource allocation and prolonged recovery periods associated with HHS management. (table 4)

Length of Stay (Days)	Total Number of Patients	Male (Number of Patients)	Female (Number of Patients)	Total Percentage	Mean ± SD (Total)	Mean ± SD (Male)	Mean ± SD (Female)
5-10 days	100	60	40	40%	7.5 ± 1.5	7.5 ± 1.5	7.5 ± 1.5
11-20 days	120	72	48	48%	15.5 ± 2.5	15.5 ± 2.5	15.5 ± 2.5
>20 days	30	18	12	12%	25 ± 3	25 ± 3	25 ± 3

Table 4. Summarized Length of Hospital Stay

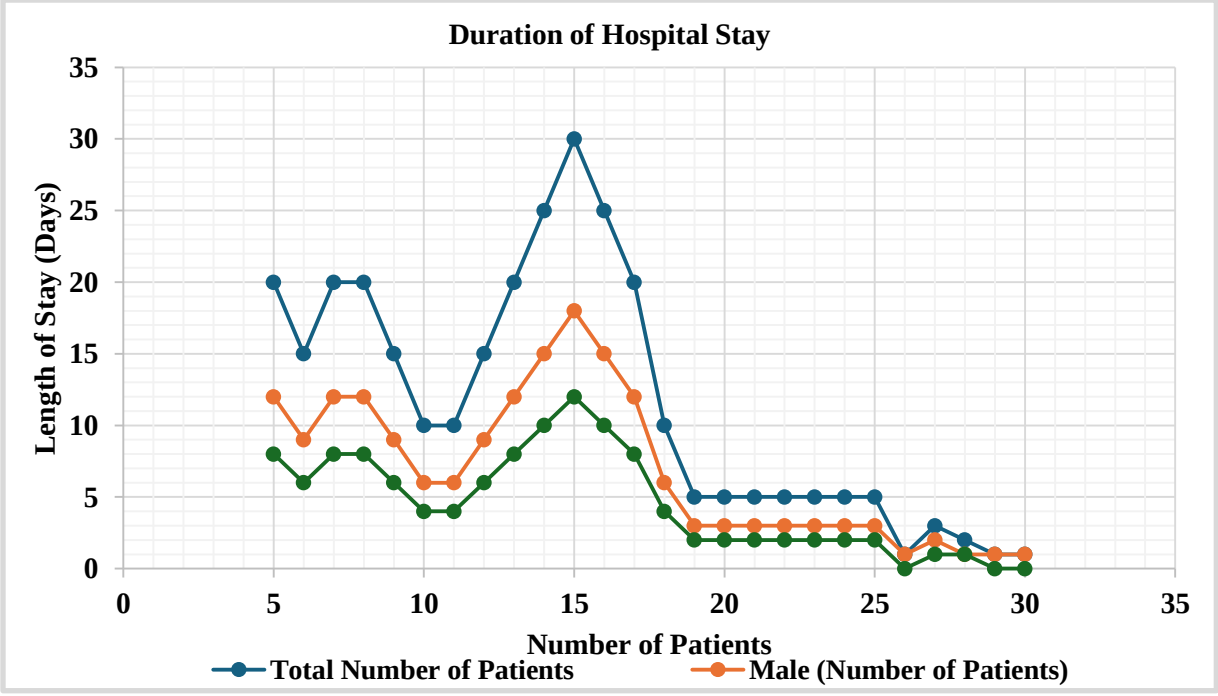

Fig. 2: Distribution of Hospital Stay Lengths for Patients

The linear graph elucidates the distribution of hospital stay lengths for HHS patients, highlighting significant gender differences. The data shows a predominance of hospital stays within the 11–20-day range, with a clear trend indicating longer durations for males compared to females. This visual representation complements the

summarized table, providing a clear and detailed illustration of hospitalization patterns and the substantial healthcare burden posed by HHS. The graph underscores the necessity for targeted interventions to reduce hospital stay lengths and improve clinical outcomes for HHS patients.

The analysis of combined precipitating factors for HHS reveals a complex interplay of medical, behavioral, and pharmacological influences. Infections were a significant precipitant, with pneumonia (40 ± 5) and urinary tract infections (35 ± 4) being notably prevalent. Behavioral factors such as medication noncompliance (150 ± 20) and dietary indiscretions (87 ± 15) were prominent, underscoring the challenges in maintaining effective diabetes management. Pharmacological influences, including corticosteroid (42 ± 10) and diuretic (38 ± 8) use, further compounded the risk. This multifactorial analysis underscores the necessity for a holistic and integrated approach to diabetes care that addresses these diverse and interrelated factors. (table 5)

Factor type	Specific Factor	Number of Patients	Percentage	Mean ± SD
Infections	Pneumonia	40	16%	40 ± 5
	Urinary Tract Infections	35	14%	35 ± 4
	Sepsis	20	8%	20 ± 3
	Skin Infections	10	4%	10 ± 2
	Other Infections	7	3%	7 ± 1
Behavioral Aspects	Medication Noncompliance	150	60%	150 ± 20
	Dietary Indiscretions	87	35%	87 ± 15
	Lack of Regular Medical Follow-Up	130	52%	130 ± 10
Pharmacological Influences	Corticosteroids	42	17%	42 ± 10
	Antipsychotics	20	8%	20 ± 5
	Diuretics	38	15%	38 ± 8
	Missed/Incorrect Dosage of Diabetes Medications	75	30%	75 ± 15

Table 5. Contributing Factors to HHS in Diabetic Patients

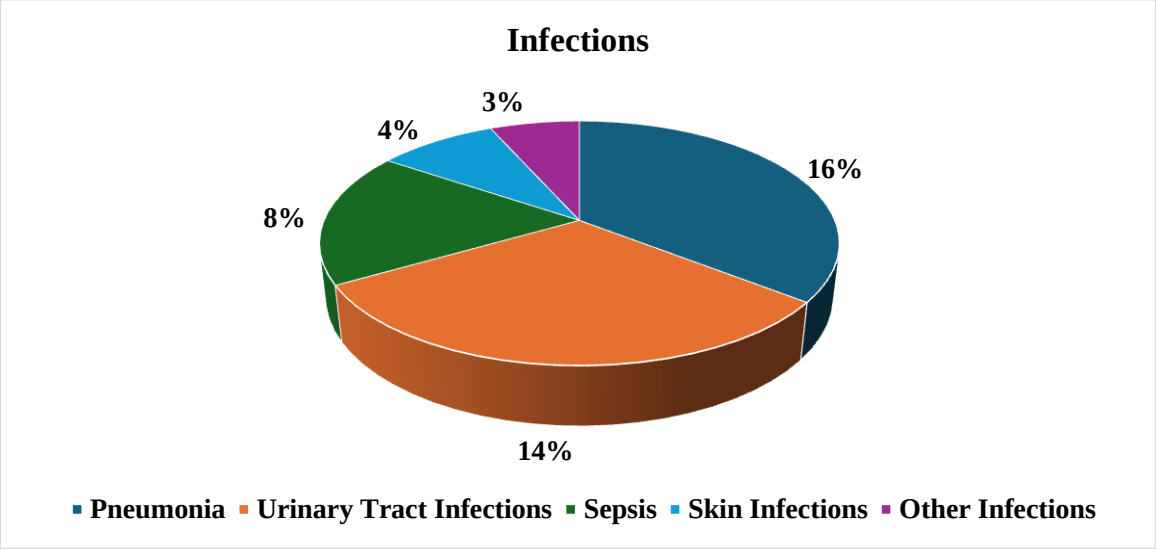

Fig. 3: The Role of Infections in Contributing to HHS

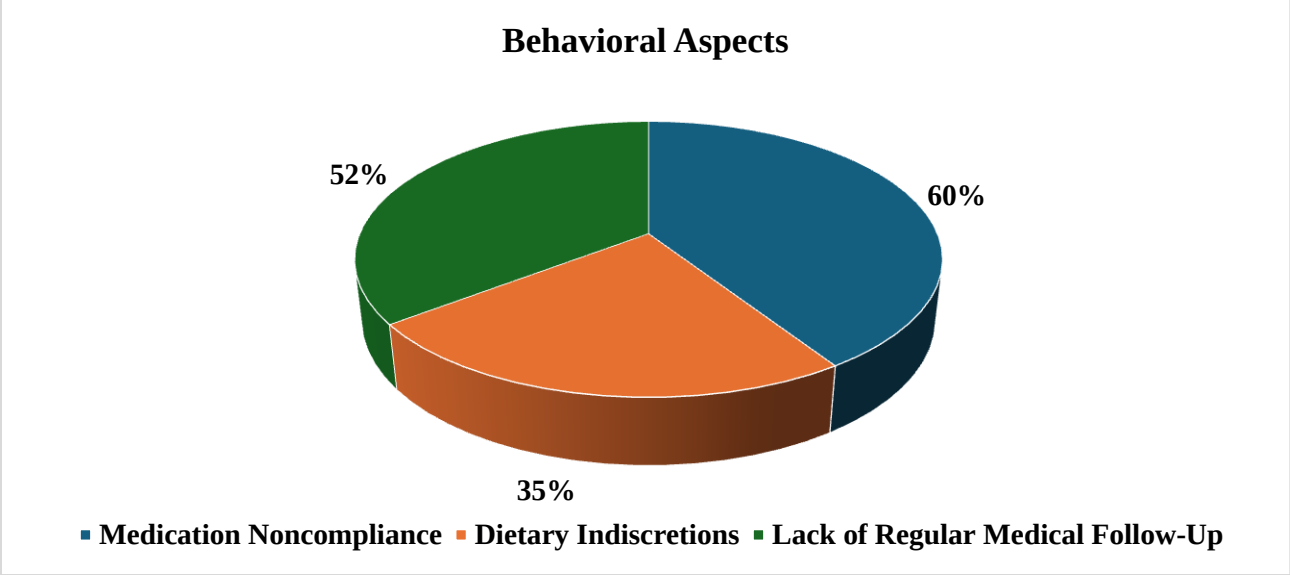

Fig. 4: The Role of Behavioral Factors in Contributing to HHS

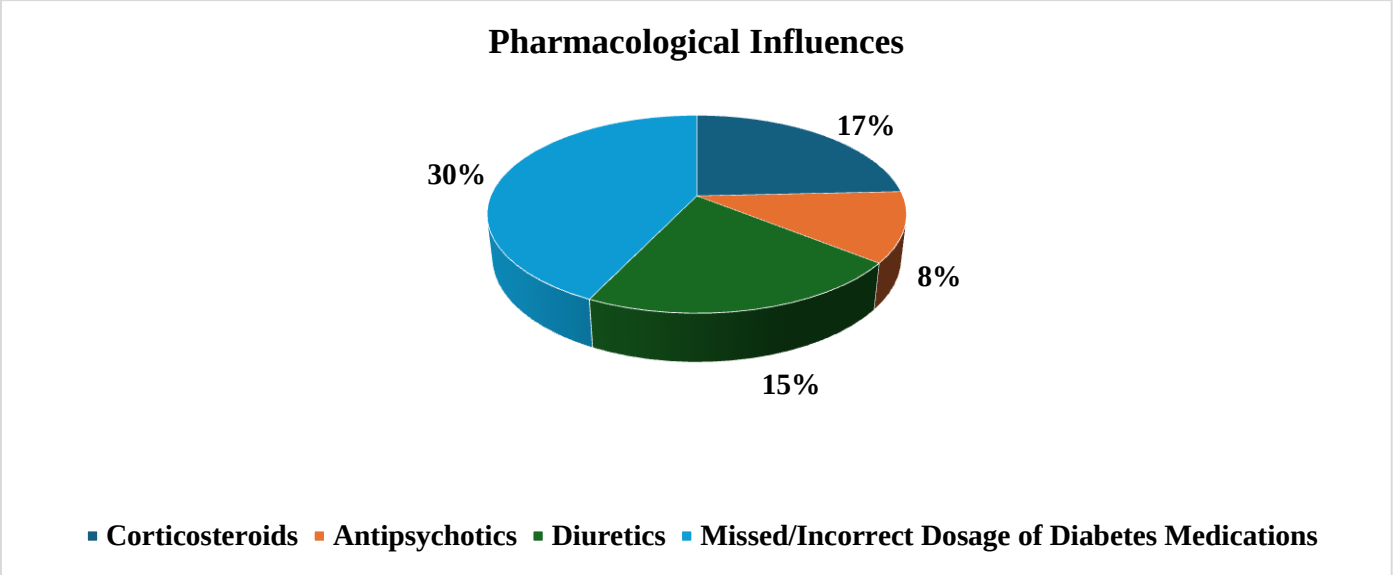

Fig. 5: Influence of Pharmacological factors in causing HHS

The comprehensive analysis of the finalized tables reveals a multifaceted and severe clinical picture of HHS among diabetic patients. The age distribution data underscores the heightened risk among middle-aged to older adults, particularly males. Laboratory findings highlight critical metabolic disturbances necessitating immediate intervention. Mortality and complication rates reflect the grave outcomes associated with HHS, with significant variability and gender differences emphasizing the need for tailored management strategies.

The length of hospital stay data points to a substantial healthcare burden, with prolonged hospitalizations particularly among male patients. The analysis of combined precipitating factors underscores the complex interplay of infections, behavioral aspects, and pharmacological influences, necessitating a holistic approach to diabetes management.

Overall, these findings emphasize the critical need for improved preventive and management strategies for HHS, focusing on comprehensive patient education, strict adherence to medication regimens, and careful monitoring of potential precipitating factors. The data underscores the importance of a multifaceted approach to mitigate the severe complications and substantial healthcare burden associated with HHS in diabetic patients.

DISCUSSION:

This study provides an in-depth analysis of the precipitating factors and outcomes of Hyperosmolar Hyperglycemic State (HHS) in diabetic patients with

poor adherence to their management regimens. Findings highlight the severe nature of HHS, underscoring the importance of multifaceted intervention strategies. [5-7]

The age distribution data indicates that middle-aged to older adults, specifically those between 51-70 years, are predominantly affected by HHS. This finding aligns with the known higher prevalence of type 2 diabetes in this age group. The slight male predominance observed suggests that gender-specific factors may influence the risk and management of HHS. This demographic insight is critical for tailoring preventive strategies and allocating healthcare resources effectively.

The laboratory results highlight extreme metabolic disturbances, with an average blood glucose level of 700 ± 100 mg/dL, reflecting acute hyperglycemia. Elevated serum osmolality and electrolyte imbalances further underscore the critical condition of these patients. These findings are consistent with the pathophysiology of HHS, where severe dehydration and hyperglycemia lead to significant physiological stress. The necessity for immediate and intensive medical intervention is evident from these biochemical abnormalities. [8-10]

The mortality rate of 12% observed in this study is comparable to other studies on HHS, which report mortality rates ranging from 10% to 20%. The high incidence of acute kidney injury (28%), electrolyte imbalances (40%), and acute respiratory distress syndrome (ARDS) (6%) highlights the severe complications associated with HHS. These outcomes underscore the critical need for early detection and comprehensive management of HHS to prevent such severe complications. [11-12]

The data on hospital stay length reveals that a significant proportion of patients required prolonged hospitalization, particularly those staying 11-20 days (48%). The gender distribution shows males had longer hospital stays across all categories. This could be due to more severe presentations or different responses to treatment, highlighting the need for gender-specific management approaches. [13]

The analysis of precipitating factors reveals a complex interplay of infections, behavioral aspects, and pharmacological influences. Infections, particularly pneumonia and urinary tract infections, were significant contributors. Behavioral factors such as medication noncompliance and dietary indiscretions were also prominent, reflecting the challenges in maintaining effective diabetes management. Pharmacological influences, including the use of corticosteroids and diuretics, further compounded the risk. These findings underscore the necessity for a holistic approach to diabetes management that addresses these diverse and interrelated factors. [14]

The results of this study are consistent with existing literature on HHS. Previous studies have similarly identified infections, noncompliance with diabetes treatment, and certain medications as primary triggers for HHS. For instance, a study by Kitabchi et al. (2009) emphasized the role of infections and medication noncompliance as major precipitating factors for HHS, which is corroborated by the findings of this study. [15]

The demographic findings, including the predominance of middle-aged to older adults and a slight male bias, align with global epidemiological trends. The high mortality and complication rates observed are also consistent with other studies, which highlight the severe outcomes associated with HHS. A study by Pasquel et al. (2014) reported similar complication rates, reinforcing the critical nature of HHS and the need for comprehensive management strategies. [16]

The length of hospital stay findings in this study are reflective of the substantial healthcare burden posed by HHS. The prolonged hospitalizations observed are consistent with studies such as that by Benoit et al. (2011), which reported similar durations of hospital stays for HHS patients. This highlights the need for effective management strategies to reduce hospital stay lengths and improve clinical outcomes. [17]

The findings of this study have several implications for clinical practice. The high prevalence of infections as a precipitating factor underscores the importance of preventive measures, such as vaccination and early treatment of infections in diabetic patients. The significant role of behavioral factors, particularly medication noncompliance, highlights the need for enhanced patient education and support systems to ensure adherence to diabetes management regimens. [18]

The severe metabolic disturbances observed necessitate immediate and intensive medical intervention. Healthcare providers should be vigilant in monitoring diabetic patients, especially those with poor adherence, for early signs of HHS. The high complication rates underscore the need for comprehensive management strategies that address not only hyperglycemia but also the associated electrolyte imbalances and organ dysfunctions. [19, 20]

The prolonged hospital stays, and high healthcare burden associated with HHS highlight the need for effective prevention and management strategies. Interventions aimed at improving adherence to diabetes management, early detection of precipitating factors, and comprehensive treatment approaches are crucial to reducing the incidence and severity of HHS.

Limitations:

This study has several limitations that must be acknowledged. The retrospective design limits the ability to establish causality and relies on the quality of existing medical records, which may be incomplete or inaccurate. Being a single-center study, the findings may not be

generalizable to other settings with different patient demographics and healthcare practices. The determination of poor adherence to diabetes management, often based on self-reported data, is susceptible to bias. Unmeasured confounders such as socioeconomic status and psychological factors were not accounted for, and variations in treatment protocols over the study period may have influenced outcomes. Additionally, the study's focus on immediate factors and short-term outcomes excludes long-term impacts, and the sample size, while substantial, may not detect fewer common factors. The exclusion of pediatric patients limits insights into this demographic, and the lack of detailed data on preventive measures implemented prior to HHS onset prevents a comprehensive understanding of effective prevention strategies. Future research should aim to address these limitations through prospective, multicenter studies with larger, more diverse populations and standardized data collection.

CONCLUSION:

This comprehensive study elucidates the multifaceted etiology and severe clinical implications of Hyperosmolar Hyperglycemic State (HHS) in diabetic patients with poor adherence to their management regimens. The findings highlight a significant burden of HHS among middle-aged to older adults, particularly males, who exhibit higher rates of hospitalizations and complications. The study underscores the critical role of infections, behavioral factors, and pharmacological influences as primary precipitating factors for HHS. Notably, infections such as pneumonia and urinary tract infections, medication noncompliance, and the use of corticosteroids and diuretics are pivotal contributors.

The high mortality rate and severe complications such as acute kidney injury, electrolyte imbalances, and acute respiratory distress syndrome (ARDS) emphasize the urgent need for effective and multifaceted management strategies. These strategies should encompass enhanced patient education, stringent adherence to medication regimens, and proactive monitoring to detect early signs of HHS. The prolonged hospital stays observed, particularly among male patients, reflect the substantial healthcare burden associated with HHS, highlighting the necessity for targeted interventions to reduce hospitalization durations and improve clinical outcomes.

Overall, this study reinforces the importance of a holistic approach to diabetes management, addressing medical, behavioral, and pharmacological components to mitigate the risk of HHS. Implementing comprehensive prevention strategies, tailored patient education programs, and regular follow-up can significantly reduce the incidence of HHS, thereby improving patient outcomes and alleviating the healthcare burden. These findings provide a critical foundation for developing targeted interventions and policies to enhance diabetes care and prevent life-threatening complications like HHS in diabetic patients.

Conflict of interest: None

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