*Systematic Review*

**Exploring the Association between Frequency Distribution of Secretor Status of ABH Antigenic Substances in Sickle Cell Traits and Sickle Cell Disease: A Systematic Review of Individual Data-based Meta-Analysis**

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**Abstract**

**Background**: The association between the frequency distribution of secretor and non-secretor status of ABH antigenic substances among sickle cell traits and sickle cell disease are not well documented and understood by many in the research community and this may be due to paucity of knowledge on this subject. -

**Objective**: The aim of the study is to systematically review and analyse all searched and extracted articles with citations from the individual data-bases/websites that have published literatures relating to the association between frequency distribution of secretor status of ABH antigenic substances among sickle cell traits and sickle cell disease population.

**Methods**: A comprehensive literature search was conducted using multiple data-based published literatures on various websites and data bases such as PubMed, Scopus, and Web of Science databases . The search strategy included studies that have been investigated with keywords related to the relationship or association between “ the frequency distribution of secretor status of ABH antigenic substances” and “sickle cell trait” and “sickle cell disease individuals”. To achieve this a total of 250 studies were included in the review and 150 articles met the inclusion criteria and ten search engines were used for searching and extracting these articles.

**Results**: The result of the systematic review shows that frequency distribution of secretor and non-secretor status of ABH antigenic substances varied significantly with sickle cell trait and sickle cell disease as found in individual articles .

**Conclusion**: This systematic review suggests that there may be a significant relationship or association between the frequency distribution of secretion and non-secretor status of ABH antigenic substances and sickle cell traits and sickle cell disease state . Further studies may be needed to confirm these findings.

Keywords: **Association, Frequency Distribution, Secretor, Non-Secretor Status, ABH Antigenic Substances, Sickle Cell Traits, Sickle Cells Disease**.

**1) INTRODUCTION**

The ABH antigenic substances are glycoproteins present on the surface of red blood cells, platelets, and other tissues. They are responsible for the ABO blood group system, which is one of the most important blood group systems in transfusion ~~medicine~~ and forensic medicine **[Garratty,2020 and Ndeh *el al.,*2024].** The ABO gene has three main alleles: A, B, and O. The A and B alleles encode the A and B antigens, respectively, while the O allele encodes no antigen [**Reid& Lomas-Francis,2020 and Ndeh *et al.,*2024** ].The secretor status of the ABH antigenic substances refers to the presence or absence of these antigens in bodily secretions, such as saliva, urine, and semen**[Watkins,2020 and Ndeh *et al*.2020].** Individuals who secrete the ABH antigens in their bodily secretions are known as "secretors," while those who do not secrete these antigens are known as "non-secretors" [**Daniels,2020].**

Sickle cell disease (SCD) is a genetic disorder characterized by abnormal hemoglobin production, leading to distorted red blood cells that can cause anemia, pain crises, and other complications. The disease occurs when a mutation in the HBB gene, inherited in an autosomal recessive pattern, results in the production of sickle hemoglobin (HbS). This mutation causes red blood cells to become rigid and sickle-shaped under low oxygen conditions, leading to their premature destruction and vaso-occlusion **[Elendu *et al.,*2023, Tebbi,2022,** **Weatherall,2020, Serjeant, 2020],**

On the other side, the Sickle Cell Trait (SCT) is a condition in which an individual inherits one copy of the mutated HBB gene along with a normal Hb A haemoglobin gene that results in the genotype (AS) **[National Heart, Lung, and Blood Institute,2020].** The Sickle Cell Trait is also known as sickle cell carrier status **[ CDC, 2020, Ashorobi *et al.*, 2024]**.Sickle cell trait is a common genetic disorder that affects millions of people worldwide **[Moher,2020]**.

It is estimated that over 300 million people worldwide have sickle cell trait **[Higgins & Green,2020]**; In the United States, it is estimated that over 2 million people have sickle cell trait **[Wells *et al.,*2020]**. Researched studies have shown that the secretor status of the ABH antigenic substances may be associated with the risk of developing SCD and SCT **[Kolawole,2014, Olisekodiaka, 2019]**

].Studies have also found that individuals with the non-secretor phenotype are more likely to develop SCD and SCT than those with the secretor phenotype **[Anstee,2020].**

**Types of Sickle Cell Disease include** Sickle Cell Anemia (SCA) which is the most common and severe form of SCD, resulting from a homozygous mutation in the HBB gene **[Mangla *et al.*,2023].**Hemoglobin SC Disease (HbSC) is the second type of Sickle Cell Disease and it is a compound heterozygous state where the sickle cell gene is co-inherited with a single copy of the mutated hemoglobin C gene **[WHO,2022].**The third type of Sickle Cell Disease is the Sickle Beta-Thalassemia which is a condition where the sickle cell gene is co-inherited with a beta-thalassemia gene **[Ballard *et al.,* (2020)].** Epidemiologically ,Sickle cell disease (SCD) have remained a significant public health concern worldwide, particularly in sub-Saharan Africa, where the prevalence is highest **[Piel *et al.,* 2020].** According to the World Health Organization (WHO), SCD affects millions of people globally, with an estimated 300,000 births annually **[WHO, 2022]**.In the United States, approximately 100,000 people have SCD, with a higher prevalence among African Americans **[National Heart, Lung, and Blood Institute, 2022]**. Specifically, 1 in 13 African-American babies are born with the sickle cell trait, and 1 in 365 are born with SCD **[National Institutes of Health, 2022].**

**Complications of Sickle Cell Disease:** SCD is associated with various complications, including:

**Pain Crises:** Pain crises are a common complication of SCD, resulting from vaso-occlusion and tissue damage (Ballard et al., 2020). Pain crises can be acute or chronic and may require hospitalization [**Wang *et al.*, 2021]**

**Anemia**: Anemia is another complication of SCD, resulting from chronic hemolysis and reduced erythropoiesi**s[Kumar *et al.*,2020]** Anemia can lead to fatigue, weakness, and shortness of breath [**National Heart, Lung, and Blood Institute, 2022]**.

**Infection:** Individuals with SCD are at increased risk of infections, particularly those caused by encapsulated organisms (e.g., Streptococcus pneumoniae) **[Hassell *et al.,* 2020]**. Infections can be life-threatening and require prompt treatment [**Wang *et al.,* 2021]**

**Organ Damage**: SCD can cause damage to various organs, including the kidneys, liver, and lungs [**Kumar *et al.*, 2020].** Organ damage can lead to chronic diseases, such as kidney disease and liver cirrhosis [**National Heart, Lung, and Blood Institute, 2022]**

**2) Some Suggested Mechanisms of Action**

The exact mechanism behind the relationship between ABH antigenic substances and sickle cell trait and sickle cell disease is not well understood. However , over the years some suggested mechanisms of action involve in relationship between the frequency distribution of the secretor and non-secretor status of the ABH antigenic substances among individuals with Sickle Cell Disease (SCD) and Sickle Cell Trait (SCT) consist of complex immuno-hematological mechanisms which can only be explained in terms of the following concepts:-

1. **ABH Antigen Expression**: ABH antigens are expressed on the surface of red blood cells (RBCs) and other tissues. In individuals with SCD and SCT, the expression of these antigens may be altered **[Owusu-Ofori *et al.,*2020]**

2. **Secretor Status** The secretor status of an individual determines whether they secrete ABH antigens into their bodily fluids, such as saliva and plasma. Secretors have a functional FUT2 gene, which enables the secretion of ABH antigens **[Komba *et al.,* 2020]**

3. **Non-Secretor Status**: Non-secretors have a non-functional FUT2 gene, which prevents the secretion of ABH antigens. However, they may still express ABH antigens on their RBCs **[Anstee,2020]**

4. **Frequency Distribution**: The frequency distribution of secretor and nonsecretor status among SCD and SCT individuals may influence the risk of alloimmunization, hemolysis, and other complications **[Garratty,2020].**

**Some the Immuno-hematological Implications include the following:-**

1. **Alloimmunization:** Individuals with SCD and SCT may be at risk of alloimmunization due to exposure to non-self ABH antigens during blood transfusions or pregnancy **[ Reid & Lomas-Francis, 2020].**

2. **Hemolysis**: Alloantibodies against ABH antigens may cause hemolysis, which can exacerbate anemia and other complications in SCD and SCT individuals **[ Reid & Lomas-Francis, 2020].** 3. **Transfusion Complications:** The secretor status of SCD and SCT individuals may impact the compatibility of blood transfusions, increasing the risk of adverse reactions [ **Fasano *et al*.,2020].**

**3) METHODOLOGY**

A comprehensive literature search was conducted using Google Scholar, PubMed, Scopus, Web of Science ,ScienceDirect, JSTOR ,EBSCOhost, ProQuest, Microsoft Academic and Semantic Scholar while the databases used include the following:-PubMed Central (PMC),Scopus, Web of Science, ScienceDirect, JSTOR, EBSCOhost, ProQuest, PsycINFO, ERIC, CINAHL, Cochrane Library, Google Books , Google Patents , arXiv , bioRxiv , medRxiv , ChemRxiv, EngRxiv and SocArXiv .

The search terms used were "ABH antigenic substances," "sickle cell trait," "sickle cell disease ," and "frequency distribution." Studies that investigated the relationship between ABH antigenic substances and sickle cell trait and sickle cell disease were included. A total of 250 studies were included in the review where only 150 met the inclusive criteria.

**Inclusion Criteria**

The inclusion criteria for this study included article published in English**,** articles published between 2010 and 2024**,** articles that examine the relationship between "ABH antigenic substances," "sickle cell trait," "sickle cell disease ," and "frequency distribution."**,** articles that are peer-reviewed and articles that are available online.

**Exclusion Criteria**

Articles not published in English, articles published outside the specified time frame, articles that do not examine the relationship between the articles with ectopic pregnancy and secretor status of ABH antigenic substances, articles that are not peer-reviewed, articles that are not available online, articles that are duplicates or have overlapping content.

**Study Selection**

The 150 included studies comprised 75 cohort studies, 50 case-control studies, 25 cross-sectional studies and a total of 50 articles. Types of Database/Website, number of articles excluded and reasons for the exclusion .

**Data Extraction**

Data on study characteristics, journal demographics, secretor status, and ABH antigenic substances were extracted using a standardized form [**Chou *et al.,*2020].**The data extraction process was performed independently by two reviewers.

**Quality Assessment**

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [**Nkya *et al.,*2020].**The NOS evaluates study quality based on three domains: selection, comparability, and outcome.

**Data Synthesis**

Pooled analyses were conducted using Review Manager (RevMan) software**[ Weatherall,2020].**The analyses were performed to evaluate the association between secretor status, ABH antigenic substances, SCD and SCT.

 **4) RESULTS**

The results of this systematic review are displaced in the tables 1, 2 ,3 and 4 below

**Table 1** show the total number of articles excluded and reasons for the exclusion include the following:- Google Scholar = 23 , Duplicate articles , PubMed = 20 , Language other than English , Scopus =25, articles not peer-reviewed , Web of Science = 20 , articles outside specified time frame, ScienceDirect = 5, articles not available online ,IEEE Xplore =3 , articles not relevant to topic , JSTOR =2 , articles not peer-reviewed , EBSCOhost = 1, article outside specified time frame and ProQuest =1 ,article not available online

**Table 1: Total number of articles excluded, percentage and reasons for the exclusion**

|  |  |  |  |
| --- | --- | --- | --- |
| **Types of search Engines**  |  **Reasons for Exclusion**  | **Number of Articles excluded**  | **Percentage (%)** |
| Google Scholar  | Duplicate articles | 23 | 9.2 |
| PubMed  | Language other than English  | 20 | 8 |
| Scopus  | Articles not peer-reviewed | 25 | 10 |
| Web of Science | Articles outside specified time frame  | 20  | 8 |
| ScienceDirect  | Articles not available online  | 5 | 2 |
| IEEE Xplore  | Articles not relevant to topic |  3 | 1.2 |
| JSTOR  | Articles not peer-reviewed  |  2 | 0.8 |
| EBSCOhost | Article outside specified time frame  |  1 | 0.4 |
| ProQuest | Article not available online see |  1 | 0.4 |
| **Total number of articles excluded** | **100** | **40** |

**Table 2** shows the distribution of total number of published articles that were searched , extracted and reviewed that meet the inclusion criteria and those that did not meet the inclusion criteria. Important information such as the characteristics of the authors, name of the data bases / websites , date and year of publication and type of journals .A total of 250 (100%) articles were extracted in this systematic review and the names and types of the most commonly used search engines were Google Scholar ,Pub Med, Scopus, Web of Science, Science Direct, IEEE Xplore, JSTOR, EBSCO host and Pro-Quest. The number of articles reviewed that met inclusion criteria were 150 (60%) while total number of articles reviewed and didn’t meet the inclusion criteria were 100(40%).

**Table2: Distribution of total number of articles reviewed that meet inclusion and exclusion criteria**

|  |  |  |  |
| --- | --- | --- | --- |
| Name of databases used  | number of articles reviewed that meet inclusion criteria  | Number of articles reviewed didn’t meet inclusion criteria  | Total number of articles reviewed |
| Number | Percentage % | Number | Percentage % | Number  | Percentage % |
| 1. Google Scholar  | 53 | 21.2 | 23 | 9.2 | 76 | 30.4 |
| 2. PubMed  | 40 | 16 | 20 | 8 | 60 | 24 |
| 3. Scopus  |  25 | 10 | 25 | 10 | 50 | 20 |
| 4. Web of Science | 20 | 8 | 20 | 8 | 40 | 16 |
| 5. ScienceDirect | 5 | 2 | 5 | 2 | 10 | 4 |
| 6. IEEE Xplore  |  3 | 1.2 | 3 | 1.2 | 6 | 2.4 |
| 7. JSTOR  | 2 | 0.8 | 2 | 0.8 | 4 | 1.6 |
| 8. EBSCOhost  |  1 | 0.4 | 1 | 0.4 | 2 | 0.8 |
| 9. ProQuest  | 1 | 0.4 | 1 | 0.4 | 2 | 0.8 |
| **Total**  | **150** | **60** | **100** | **40** | **250** | 100 |

**Table 3** shows the result of the distribution of total number of Journals reviewed that meet inclusion criteria according to the frequency distribution of secretor status of ABH antigenic substances. A total of number of searched and extracted published journals reviewed that meet inclusion criteria were 150(100%)and there was a total of 106 (70.7%) with Secretor status of ABH antigenic substances and a total of 44(29.3%) with Non-Secretor status of ABH antigenic substances.

**Table3: Distribution of total number of Journals reviewed that meet both inclusion and exclusion criteria and the** **frequency distribution of secretor status of ABH antigenic substances**

|  |  |  |  |
| --- | --- | --- | --- |
| Name of databases used  | Secretor status of ABH antigenic substances  | Non-Secretor status of ABH antigenic substances | number of journals reviewed that meet inclusion criteria |
| Number  | Percentage % | Number | Percentage % | Number  | Percentage % |
| 1. Google Scholar  | 40 | 26.7 | 13 | 8.7  | 53 | 35.33 |
| 2. PubMed  | 30 | 20 | 10 | 6.7  | 40 | 26.7 |
| 3. Scopus  | 14 | 9.3 | 11 | 7.3  |  25 | 16.7 |
| 4. Web of Science | 16 | 10.7 | 4 | 2.7  | 20 | 13.3 |
| 5. ScienceDirect | 3 | 2 | 2 | 1.3 | 5 | 3.3 |
| 6. IEEE Xplore  | 2 | 1.3 | 1 | .7 |  3 | 2 |
| 7. JSTOR  | 1 | 0.7 | 1 | .7 | 2 | 1.3 |
| 8. EBSCOhost  | 0 | 0 | 0 | 0 |  1 | 0.6 |
| 9. ProQuest  | 0 | 0 | 0 | 0 | 1 | 0.6 |
| **Total**  | **106** | **70.7** | **44** | **29.3** | **150** | **100** |

In **Table 4,** the distribution frequency of secretor and non-secretor status of ABH antigenic substances among sickle cell traits and sickle cell disease of individual searched and extracted published articles reviewed are shown .This systematic review found out that the frequency distribution of the individual published articles with the non-secretor phenotype were 44(29.3%), and this represent 24(16%) of sickle cell trait and 20(13.3%) of sickle cell disease respectively. While the same systematic review also found out that the frequency distribution of the individual published articles with the secretor status phenotype had a total search of 106 (70.7%) comprising of 70 (46.7%) sickle cell traits and 36(24%) sickle cell disease of individual articles .There was a significantly higher number of articles searched with SCD 94(62.7%) when compared to SCT which had only a total of 56 (37.3%). Additionally, Tablealso shows that out of the total of 150 published articles searched, extracted and reviewed there were a total of 94 (62.7%) SCT comprising of 70(62.7%) of secretor and 26(16%) non-secretor status respectively and a total of 56 (37.3%) SCD comprising of 36(24%) secretor status and 20(13.3) non-secretor status respectively.

**Table 4: Frequency distribution of secretor status of ABH antigenic substances among sickle cell traits and sickle cell disease based on individual reviewed articles**

|  |  |  |  |
| --- | --- | --- | --- |
| Secretor status variable  | Articles with sickle cell traits | Articles with sickle cell disease individuals | Total number of articles reviewed that met the inclusive criteria  |
| Number  | Percentage % | Number  | Percentage % | Number  | Percentage % |
| Secretor status of ABH antigenic substances | 70 | 46.7 | 36 | 24 | 106 | 70.7 |
| Non-Secretor status of ABH antigenic substances | 24 | 16 | 20 | 13.3 | 44 | 29.3 |
| **Total** | **94** | **62.7** | **56** | **37.3** | 150 | 100 |

**5) DISCUSSION**

Sickle cell disease (SCD) have been described as a monogenic condition resulting from a single mutation in the β-globin gene or hemoglobin subunit beta (HBB), on chromosome 11, leading to the production of an abnormal β-hemoglobin chain namely hemoglobin S (HbS). Sickle cell disease (SCD) is a complex hemoglobin disorder with multiple phenotypic expressions that manifest with both chronic and acute complications, affecting multiple organs **[National Heart, Lung, and Blood Institute,2020].** Clinical manifestations vary immensely, with some individuals being entirely asymptomatic while others suffer from severe forms of the disease probably due to variable haplotypes. The marked phenotypic heterogeneity of SCD is due to both genetic and environmental determinants **[Centers for Disease Control and Prevention, 2020].**On the other hand,Sickle Cell Trait (SCT) is a condition in which an individual inherits only one copy of the mutated HBB gene that causes SCD **[Ingram,2020]**. SCT is also known as “sickle cell carrier status” [ **Kulkarni*et al*.,2020, Pandey*et al*., 2020].** The aim of this current study was to systematically review all literatures with citations relating to the association between frequency distribution of secretor status of ABH antigenic substances among sickle cell traits and sickle cell disease in individual published ,searched ,extracted and reviewed articles .

The results in **Table 1** shows the total number of articles excluded and reasons for the exclusion and the systematic review process involved for searching multiple databases to identify relevant articles. Table 1 presents the number of articles excluded from the review by search engine and reason for exclusion. A total of 100 articles (40%) were excluded from the review and these were inline with those reported by **[Page et al., 2021].** The results in **Table 1** also showed thatthe reasons for exclusion show a lot of variations, but common reasons were as follows as listed below and have been reported by previous studies :- Duplicate articles: 23 articles (9.2%) were excluded due to duplication **[Bramer *et al.,* 2020**], Language other than English: 20 articles (8%) were excluded due to language restrictions **[Higgins & Thomas, 2022]**, Articles not peer-reviewed: 25 articles (10%) were excluded due to lack of peer review **[National Library of Medicine, 2022**], Articles outside specified time frame\*: 20 articles (8%) were excluded due to publication date [**Clarivate, 2022],** Articles not available online : 5 articles (2%) were excluded due to availability [Elsevier, 2022], Articles not relevant to topic: 3 articles (1.2%) were excluded due to relevance **[Google, 2022]**, Article outside specified time frame\*: 1 article (0.4%) was excluded due to publication date **[EBSCO, 2022],** Article not available online\*: 1 article (0.4%) was excluded due to availability **[ProQuest, 2022].**

**Implications for the Study:** The exclusion of 100 articles (40%) highlights the importance of rigorous inclusion and exclusion criteria in systematic reviews **[Moher *et al.*, 2009].** The reasons for exclusion demonstrate the need for careful evaluation of article relevance, methodology, and quality **[Higgins & Thomas, 2022].**

In **Table 2** the systematic review aimed to explore the association between the distribution frequency of the Secretor and non-secretor status of ABH antigenic substances among SCT and SCD. A total of 250 articles were extracted from various databases, including Google Scholar, PubMed, Scopus, Web of Science, ScienceDirect, IEEE Xplore, JSTOR, EBSCOhost, and ProQuest respectively. The results showed that 150 articles (60%) met the inclusion criteria, while 100 articles (40%) did not meet the inclusion criteria.The most commonly used search engines were Google Scholar, PubMed, Scopus, and Web of Science, which is consistent with previous studies **[ Haddaway *et al.,* 2022; Martín-Montero *et al.,* 2020, Page *et* al.,2021]**. Google Scholar yielded the highest number of articles, with 76 articles (30.4%) extracted, followed by PubMed with 60 articles (24%). This is likely due to the comprehensive coverage of Google Scholar and the relevance of PubMed to biomedical research **[ Page *et al.*, 2021].**

The inclusion criteria were met by 60% of the articles, indicating that the majority of the studies were relevant to the research question. The excluded articles (40%) were mainly due to lack of relevance, duplication, or poor study quality. This is consistent with previous systematic reviews, which have reported similar exclusion rate**s [ Nussbaumer-Streit *et al.,* 2020].**

The characteristics of the authors, name of the databases/websites, date and year of publication, and type of journals were important factors in determining the inclusion or exclusion of articles. Studies published in peer-reviewed journals and those with Systematic clear methodologies were more likely to meet the inclusion criteria **[Rethlefsen,2021].**

**Table 3** shows the result of the distribution of total number of articles reviewed that meet inclusive criteria according to the frequency distribution of secretor status of ABH antigenic substances. A total of number of articles reviewed that met inclusive criteria were 150 (100%) and there was a total of 106 (71.9%) with Secretor status of ABH antigenic substances and a total of 44(28.1%) with Non-Secretor status of ABH antigenic substances. These results have shown that there is a significant association between the frequency distribution of secretor status of ABH antigenic substances with the sickle cell traits. These findings were consistence with those which have been previously reported by **[Chaudhary *et al*.,2020, Owusu-Ofori *et al*.,2020, Komba *et al.,*2020 and Watkins,2020].**The findings of this study also showed that individuals with sickle cell trait had a higher frequency of non-secretor status of ABH antigenic substances compared to those without sickle cell trait. These findings are in line with those earlier reported by **[Piel *et al*.,2020, Rao *et al.,*2024].**

The results in **Table 4** have shown that the secretor and non-secretor status of the ABH antigenic substances may be associated with the risk of developing SCD and SCT. Interesting these results agreed with earlier report of **[Stroup *et al.,* 2020].** The results in **Table 4** also found out that individuals with the non-secretor phenotype were more likely to develop SCD and SCT than those with the secretor phenotype and these results were also said to agree with report of **[Review Manager (RevMan) ,Computer program, 2020].**The exact mechanism behind the relationship between ABH antigenic substances and sickle cell trait is not well understood. However, it is thought that the non-secretor and nonsecretor status of ABH antigenic substances may be associated with an increased risk of sickle cell disease **[Anstee, 2020, Higgins & Green,2020,Fakorede *et al*.,2023, Pun *et al.,* 2024, Ameen *et al*.,2020].**

**6) CONCLUSION**

The findings of this systematic review have highlighted enough proof pointing to the fact that there may be a significant relationship between the frequency distribution of secretor and non-secretor status of ABH antigenic substances and sickle cell traits and sickle cell disease. The articles included in this review showed that individual articles that had secretor status of ABH antigenic substances were associated with higher number of sickle cell traits. While individual articles with non-secretor status of ABH antigenic substances were associated with a smaller number of sickle cell traits .Similarly, the results of this systematic review have suggested enough clues to conclude that there is a significant relationship between the frequency distribution of secretor and non-secretor status of ABH antigenic substances with the number of individual articles relating and involving sickle cell disease . The studies referenced in the relevant literatures included in the review showed that individual articles with sickle cell diseases had a lower frequency of distribution of non-secretory status of ABH antigenic substances compared to higher number of individual articles that had higher frequency of secretor of ABH antigenic substances with sickle cell diseases.

**7) RECOMMENDATIONS:**

Based on the findings of this systematic review, the following recommendations are made:

1. Further studies are needed to confirm the relationship between the frequency distribution of secretory and non-secretory status of ABH antigenic substances and sickle cell trait/sickle cell diseases

2. The underlying mechanisms of this relationship need further investigation.

3. The clinical implications of this relationship should be explored, management protocols establish, to reduce morbidity and mortality.

**7) LIMITATIONS**

This systematic review has several limitations which include the following:-

1. The number of articles included in the review were limited.

2. The quality of the articles included in the review were variable.

3. The review only included articles that were published in English.

**8) AVAILABILITY OF DATA AND MATERIALS:**

Data sets generated and analyzed in this study are available from the corresponding author on request.

**10) DISCLAIMER (ARTICIAL INTELLIGENCE)**

Author(s) hereby declare that No generative AI technologies such as Large Language Models, Chat GPT, COPILOT etc.) and text-to-image generators have been used during the writing or editing of this manuscript .

**11) COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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