Amiodarone Induced Myxedema Coma: A Systematic Review of Case Reports

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Research Article

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Abstract

Objective

The current systematic review examined whether elderly patients who received amiodarone were at risk for developing myxedema coma.

Methods

The Cochrane guidelines were used for a systematic review of Medline (PubMed), Science Direct, CINAHL Cochrane database, and Google Scholar for case reports on the Amiodarone-induced myxedema coma.

Results

A total of 12 case reports were found to meet the determined inclusion criteria. Patients who received amiodarone highly risk of developing myxedema coma. Case reports showed that patients received 100–200 mg of amiodarone orally and developed bradycardia and hypothermia with elevation in thyroid stimulating hormone. Most patients were treated with levothyroxine and hydrocortisone medication upon diagnosis.

Conclusion

The various possible causes of Myxedema coma make diagnosis difficult. Through clinical symptoms and serum TSH, the diagnosis could be confirmed. Amiodarone-induced Myxedema coma was successfully treated with levothyroxine and glucocorticoids.

Introduction

Myxedema coma is a rare serious condition due to prolonged hypothyroidism and poor homeostasis maintenance [1]. Myxedema Coma is a potentially fatal hypothyroidism symptom that includes signs of altered mental status, hypothermia, and another organ system slowdown [2, 3]. In people with poorly controlled hypothyroidism, A significant death rate and an exceptionally unusual final stage of severe hypothyroidism are linked to myxedema coma [4]. It can result from severe, protracted hypothyroidism or be brought on by sudden stressors like an illness, a myocardial infarction, exposure to a cold, or surgery [5]. This potentially fatal condition affects 0.22 per million persons annually and is more prevalent in women over 60 [6]. Up to 25% of patients may experience focal or generalized seizures. In addition, signs of hypothermia, electrocardiographic abnormalities, cardiomegaly, decreased cardiac output, and hypotension may be present. Respiratory depression causes progressive hypoxemia and hypoventilation. Gastrointestinal symptoms include anorexia, stomach pain, and constipation with feces retention. In

addition to impaired intestinal motility, paralytic ileus, and megacolon, there may be a distended abdomen [3].

Given a patient with a history of or physical signs compatible with hypothyroidism in the presence of stupor, disorientation, or coma, especially in hypothermia, the probable diagnosis of myxedema coma should be easy to make. A prevalent misunderstanding is that patients cannot be diagnosed with a myxedema coma until they are comatose; however, neither edema nor coma is typically presented in patients [3]. Thyroid-stimulating hormone (TSH) and free T4 are the most popular laboratory test for assessing thyroid function. The serum T4 level in MC is typically very low. The serum TSH level may be low, normal, or slightly high, indicating central hypothyroidism, or high, indicating primary hypothyroidism [7]. Despite all the previous notes, many other causes could induce myxedema coma, such as schizophrenia patients treated with lithium carbonate. Hence, the updated recommendation suggests that before and throughout lithium therapy, the thyroid should be periodically checked. If hypothyroidism starts, the medicine should be stopped, and the proper treatment should be started [8]. Nivolumab is a monoclonal antibody that treats lung cancer, metastatic melanoma, relapsed Hodgkin lymphoma, and renal cell cancer, which has also been found to induce myxedema coma. It should be stopped in patients with severe hypothyroidism but can be restarted if stabilized [9].

Also, if Amiodarone doses are greater than 200 mg/day, amiodarone-induced myxedema coma (AIM) or hypothyroidism is observed three months to 2 years after the drug starts (Kuroski et al., 2019). cases of a myxedema coma under amiodarone therapy with no previous history of thyroid disease were reported [10].

A class III antiarrhythmic medication with a high level of efficacy, amiodarone, is frequently used to treat supraventricular and ventricular arrhythmias; it is also recognized as providing additional benefits to individuals with left ventricular systolic dysfunction [11]. However, when used frequently, amiodarone has several negative effects on the thyroid and other organ systems due to its highly iodinated chemical composition that raises the possibility of thyrotoxicity. Amiodarone has been reported to cause thyroid dysfunction in 15–20% of patients [12]. It has been proposed that AIM causes hypothyroidism; however, many cases stay misdiagnosed [13, 14]. This systematic review examines if elderly patients who received Amiodarone are at risk for developing AIM.

The Research Question

The Population, Issue of Interest, Comparison, Outcome, and Timeframe (PICOT) framework guided the research question. The research question for this systematic review: is elderly patients who received amiodarone at risk for developing AIM?

Methods

Data sources and search strategy

The authors followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report this study. A systematic review of Medline (PubMed), Science Direct, CINAHL Cochrane database, and Google Scholar was performed to investigate the risk of developing myxedema coma in patients given amiodarone. Myxedema coma, amiodarone, induced, and side effects were all search terms used in this review. A limit on either English language and year of publication between (2016 and 2022) was imposed. All possible keyword combinations were searched, and a manual literature search was conducted. As an example of a literature search, as the following search terms: (myxedema coma) AND (induced) AND (Amiodarone), (myxedema coma) AND (amiodarone) AND (side effect) OR (adverse effect), ((myxedema coma) AND (amiodarone)) AND (side effect), ((myxedema coma) AND (Amiodarone)).

Ethical Consideration

This literature review did not require the approval of an institutional review board. Instead, the investigation follows the principles outlined in the Helsinki Declaration [15].

Study Selection And Eligibility

The (PICOT) framework guided the inclusion criteria. The following case reports were considered for inclusion in the review: The population was elderly patients; the intervention is receiving amiodarone; the control is inapplicable for our study; and the outcome is myxedema coma caused by amiodarone. In addition, patients with mental illnesses were excluded. To ensure study eligibility, the authors independently screened the titles and abstracts returned by the searches. If there were any disagreements among researchers about the titles of any study, or the abstracts needed to provide more information, the full text (available and requested) was reviewed to determine if the paper met the inclusion criteria. The full texts (available and requested) of all publications that were determined to meet standards potentially were then examined to determine final inclusion. Any disagreements between reviewers were accepted through consensus or the addition of a third reviewer.

Data Extraction And Synthesis

This review was registered in the PROSPERO databases (CRDXXXXXXXXXXX). All our findings are case reports only. Two Reviewers reviewed each study, and disagreements about data abstraction were resolved through consensus or by a third reviewer. Based on data abstraction elements, data were summarized in numeric form.

Results

The study deletion process is shown in Fig. 1. Our literature search yielded 233 abstracts, of which 36 were found eligible based on initial screening and therefore underwent full-text review. Of the 36 case

reports, 5 met the inclusion criteria and were included in the final evaluation. By analyzing the study characteristic, most patients were female (N = 8, 66.7%), and most patients' age interval was 65–75 years old (41.6%). Also, the cases were reported in the USA, representing 75% of the case reports. Further, nine case reports (75%) of cases received care in the emergency department. Regarding the patient's condition, most cases had atrial fibrillation (Table (1)).

[Please insert Table 1 here]

Table 1
Characteristics of literature included in the review (N = 12)

	N	%
Gender		
Female	8	66.7%
Male	4	33.3%
Age group		
65–75 years old	5	41.6%
76–86 years old	4	33.3%
87–97 years old	3	25%
Country		
USA	9	75%
SPAIN	1	8.3%
Portugal	2	16.6%
Department of care		
ER	9	75%
Internal Medicine Department	2	16.6%
ICU	1	8.3%
Years of Publishing		
2016–2018	4	33.3%
2019–2022	8	66.7%
Chronic medical history		
Atrial fibrillation & other illnesses	6	50%
Heart failure & Atrial fibrillation	3	25%
Atrial fibrillation only	1	8.3%
Other diseases only	2	16.6%

The current reviews used the Joanna Briggs Institute (JBI) critical appraisal tool for the included case reports. This tool consists of eight questions that include four possible choices (Yes, No, Unclear, not applicable), and each question was concise and clearly defined. The critical appraisal result for the case

report shows a good quality of research evidence. One study scored (100%) for all questions [10], and four case reports scored 87.5% [2, 16]. Also, five case reports scored 75% [17–21]. However, only one study scored 62.5% [22], as well only one study scored 50% [23]; see Table (2).

[Please insert Table 2 here]

Table 2
JBI critical appraisal tool for case reports

Authors (Year)	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Percentage
Martins et al., (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Villalba et al., (2019)	Yes	Yes	Yes	Yes	unclear	Yes	No	Unclear	62.5%
Bui & Lazarus (2016)	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	75%
Gonuguntla et al., (2020)	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	75%
Kim & Syed (2020)	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	75%
Hawatmeh et al., (2018)	Yes	Yes	Yes	No	No	No	No	Yes	50%
Armaghan et al., (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	87.5%
Zagorski et al., (2020)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87.5%
Kuroski et al., (2019)	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	75%
Rana & Ahmed (2019)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	75%
Khdeir et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87.5%
Santos et al., (2017)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	87.5%

The abstracted data, including the study sample, setting, conclusion, and recommendation for all case reports, are presented in Table (3).

[Please insert Table 3 here]

Table 3
Summary of Reviewed Studies

Author name (year)	Design/ sample	Settings	Conclusion	Recommendation
Armaghan et al., (2020)	Case report one patient	Department of emergency medicine	Hypothyroidism brought on by a history of amiodarone medication can place a patient at a greater risk of developing MC.	It is significant to highlight that patients receiving long-term amiodarone medication should be continuously monitored for any indications of thyroid disease by thyroid panels.
Zagorski et al., (2020)	Case report one patient	Department of Internal Medicine	In this situation, we assume that amiodarone uses over a prolonged period of time caused his thyroid impairment.	We recommend that older persons taking amiodarone consider thyroid function testing. Healthcare providers acknowledge myxedema coma as a potential diagnosis for amiodarone usage.
Kuroski et al., (2019)	Case report one patient	Emergency department	In the literature, patients who experienced myxedema coma reported using amiodarone for three months and two years. However, this is the first case report of rapidly induced myxedema coma caused by amiodarone in a patient with an increased TSH.	When starting patients on amiodarone in the presence of an increased TSH, caution is required.
(Bui & Lazarus, 2016)	Case report one patient	Emergency department	We present a case of hypothyroidism brought on by amiodarone that appeared as hypothermia.	NA
Gonuguntla et al., (2020)	Case report one patient	Emergency department	As early diagnosis and treatment would enhance outcomes, it is crucial to consider amiodarone-induced myxedema coma when making a differential diagnosis for patients who report altered mental status or hypothermia while using amiodarone.	When using amiodarone, patients should have their thyroid function tests thoroughly monitored for the first year.
Khdeir et al. (2020)	Case report one patient	Emergency department	A few cases of people using amiodarone have been found to have a myxedema coma as a serious emergency.	Before administering amiodarone, it's crucial to assess thyroid function.

Author name (year)	Design/ sample	Settings	Conclusion	Recommendation
Santos et al., (2017)	Case report one patient	Emergency department	Patients on amiodarone medication may get severe episodes of thyroid dysfunction.	Thyroid function monitoring in amiodarone-treated patients is significant.
(Rana & Ahmed, 2019)	Case report one patient	Emergency department	Myxedema coma manifested in this patient 12 months after initiating amiodarone.	NA
Hawatmeh et al., (2018)	Case report one patient	Emergency department	Our case reports further contribute to the literature and show that amiodarone significantly contributes to thyroid dysfunction, including hypothyroidism and myxedema coma.	While treating patients receiving amiodarone medication, medical professionals should be alert for thyroid dysfunction because early detection and management are crucial to achieving the best results.
Martins et al., (2017)	Case report one patient.	Emergency department	Depend on history and physical assessment findings such as bradycardia, hypotension, generalized edema, hypothermia, and hypoventilation with respiratory acidosis and supported by laboratory test of thyroid function (elevated TSH and low T4) help in early recognition of myxedema coma. Early start of adequate thyroid replacement therapy and corticosteroids, besides supportive measures, were necessary for the success of the treatment.	Focuses on future studies on treatment as the best thyroid hormone replacement therapy in myxedema coma patients. Patients under amiodarone therapy need close observation for any changes in thyroid function. Increase awareness about amiodarone-induced hypothyroidism to prevent myxedema coma that, considers a life-threatening condition.

Author name (year)	Design/ sample	Settings	Conclusion	Recommendation
Villalba et al., (2019)	Case report 3 female, and one male patient	Department of Internal Medicine	Myxedema coma is an uncommon clinical condition associated with great mortality if not treated. All patients that present with bradycardia, bradypnea, hypoxemia, and elevated CPK should know thyroxin levels immediately to confirm the medical diagnosis and have baseline data before beginning treatment.	Hormone replacement therapy with T3 and T4 is preferred in a patient with past used amiodarone in treatment.
(Kim &Syed, 2020)	Case report one patient	ICU	Lethargy and disturbed mental status are nonspecific symptoms of myxedema coma that can occur without the more obvious skin abnormalities or myxedematous soft tissue alterations. There are no established treatment guidelines for myxedema coma. Despite the fact that the mainstays of therapy continue to be intravenous hydrocortisone and intravenous levothyroxine	Conduct additional research on how T3 must be administered in accordance with the procedure for treating Myxedema coma that has not yet developed. It is crucial for doctors to consider myxedema coma as one of the differential diagnoses in patients on amiodarone who have an underlying thyroid condition. Polypharmacy should be considered while giving amiodarone to elderly patients with thyroid issues.

By summarizing the included case reports, seven cases (58.3%) pointed out that 200 mg of amiodarone was prescribed [2, 10, 18, 20, 23–25], while four case reports (33.3%) did not mention the dose [16, 17, 22, 26]; see Table (4).

Altered mental status was also represented in ten case reports (34.5%) [10, 16, 17, 20–26], and eight cases (27.6%) reported bradycardia as a subsequent recurrent symptom among patients [2, 10, 16, 18, 22, 24–26]. However, hypothermia and hypotension were reported about in half of the cases. Additionally, nine cases (75%) reported that the patients had no previous thyroid dysfunction [10, 17, 20, 21, 23, 25, 26], while three case reports (25%) their patients had hypothyroidism [18, 22, 24]. Half of the included cases (50%) reported T3 and T4 levels [2, 17, 20, 21, 24, 25], while the remaining did not [10, 16, 18, 22, 23, 26].

For TSH, almost all cases reported the TSH level. Four cases (33.3%) pointed out TSH results between 50 and 100 mIU/L [16, 18, 22, 25], the other four reported more than 100 mIU/L [2, 20, 21, 24], and three (25%) reported TSH between 14 and 44 mIU/L [10, 17, 26]. Upon diagnosis with myxedema coma, treatment in hospitals includes levothyroxine and hydrocortisone. Different doses of levothyroxine were reported in seven cases; four cases (33.3%) pointed out 200 mcg, and three cases in each study had different doses, including 75mg [26], 100mg [24], and 250 mg [16]. However, five cases (41.6%) didn't mention the dose of levothyroxine [2, 17, 21–23]. For hydrocortisone dose, seven cases mentioned the prescribed dose; three cases (25%) pointed out 100 mg of hydrocortisone [10, 18, 24], as well two cases (16.6%) pointed out 50 mg [25, 26], and one study (8.3%) pointed out 200 mg of hydrocortisone [16]. On the other hand, five case reports did not mention the dose of hydrocortisone [2, 17, 20–23].

[Please insert Table 4 here]

Table 4
Result of the review

	Number of studies	%	Reference
Dosage and route of Amiodarone			
200 Mg P.O	7	58.3%	[2, 10, 18, 20, 23–25]
100 Mg P.O	1	8.3%	[21]
Not reported	4	33.3%	[16, 17, 22, 26]
Most common Symptoms *			
Altered mental status	10	34.5%	[10, 16, 17, 20–26]
Bradycardia	8	27.6%	[2, 10, 16, 18, 22, 24–26]
Hypotension	5	17.2%	[2, 10, 20, 22, 24]
Hypothermia	6	20.7%	[2, 10, 16, 18, 22, 25]
Previous thyroid dysfunction			
Yes	3	25%	[18, 22, 24]
No	9	75%	[10, 17, 20, 21, 23, 25, 26]
Reporting (T3 & T4) Level			
Yes	6	50%	[2, 17, 20, 21, 24, 25]
No	6	50%	[10, 16, 18, 22, 23, 26]
Thyroid serum level (TSH)			
14–44	3	25%	[10, 17, 26]
50–100	4	33.3%	[16, 18, 22, 25]
> 100	4	33.3%	[2, 20, 21, 24]
N/A	1	8.3%	[23]
Treatment in the hospital upon diagnosis			
1- Levothyroxine			
75 Mg I.V	1	8.3%	[24]
100 mcg I.V	4	33.3%	[10, 18, 20, 25]
200 mcg I.V	1	8.3%	[16]
250 mcg I.V	1	8.3%	[26]

	Number of studies	%	Reference
NA	5	41.6%	[2, 17, 21–23]
2- Hydrocortisone			
50 Mg I.V	2	16.6%	[25, 26]
100 Mg I.V	3	25%	[10, 18, 24]
200 Mg I.V	1	8.3%	[16]
NA	6	50%	[2, 17, 20–23]

Note: * Multiple responses item.

Discussion

Myxedema coma is a syndrome caused by a severe thyroid hormone deficiency. Amiodarone is an iodinated derivative of benzofuran that can cause hypo- or hyperfunction of the thyroid. On the other hand, myxedema caused by amiodarone therapy is extremely rare [27]. In the current review, the precipitating factor that led to the development of myxedema coma was a history of amiodarone therapy [2, 10, 16, 17, 24–26].

The incidence of AIM coma has been reported to range from 4–34% [28, 29]. Female gender, older age, an underlying autoimmune thyroid disease, elevated baseline TSH levels, a starting dose of amiodarone greater than 200 mg/day, complex cyanotic heart disease, and residence in an iodine-sufficient region (e.g., the United States) are all risk factors for AIM [30–32]. Patients with myxedema coma in our review study were mostly female, older than 75 years, resided in an iodine-sufficient region (the United States), had atrial fibrillation, and started on amiodarone (200 mg/day).

The diagnosis of AIM depends on clinical manifestation (mental status, hypothermia, cold exposure, infection, drugs (diuretics, tranquilizers, sedatives, analgesics), trauma, stroke, heart failure, gastrointestinal bleeding), history or current amiodarone ingestion and the thyroid function tests [33, 34]. Similarly, in the current review, most of the case reports showed the patients had elevated TSH, and 50% of the cases found that the patients had depressed T3 and T4 levels. Also, in three case reports in our review, the patients had a previous thyroid dysfunction (hypothyroidism). A mildly depressed thyroid panel with elevation in TSH was reported in the current review. It is critical to note that signs of thyroid dysfunction, as detected by thyroid panels, should be closely monitored in patients receiving chronic amiodarone therapy.

Patients with myxedema coma have common signs and symptoms such as hypothermia, bradycardia, hypotension, congestive heart failure, and hypoventilation with hypercapnia and respiratory acidosis [1, 19]. Altered mental status, bradycardia, hypotension, and hypothermia are the most recurrent symptoms

presented in our review for a patient diagnosed with myxedema coma who was on amiodarone, assessed by Glasgow coma Scale and hemodynamic stability. The various possible causes of myxedema coma make diagnosis difficult. The symptoms of AIM are difficult to detect, especially in elderly patients with a history of heart disease. However, once diagnosed, often through clinical symptoms and serum TSH, this disease must be treated with thyroid hormone right away. Myxedema coma was successfully treated with levothyroxine and glucocorticoids, as presented in the included cases.

Myxedema coma is treated with hormone replacement therapy and supportive therapy. However, many countries still need to establish evidence-based treatment for Myxedema coma because the disease is rare, and there is a lack of research in this area. Specific therapy entails giving levothyroxine [35, 36], and most of the cases in the current review considered a maintenance dose of 100–200 g/day. Because absorption from the gut is unpredictable, the first dose should be administered intravenously, and this is consistent with all findings in this review that revealed levothyroxine was administered intravenously.

Myxedema treatment is associated with a risk of relative adrenal insufficiency; thus, glucocorticoid supplementation is needed [1, 37]. In this review, five cases reported that glucocorticoid supplementation with hydrocortisone at 50–200 mg was administered intravenously. In addition, in this review, all cases reported that the patients received levothyroxine despite still taking amiodarone. This is supported by the current evidence suggesting that amiodarone can be continued in patients taking levothyroxine [34, 38, 39].

Moreover, it is critical to provide respiratory support through intubation, controlled mechanical ventilation, and supplemental oxygen therapy. Although the patient is hypothermic, external warming should be avoided because it can cause peripheral vasodilation and circulatory collapse. At room temperature, however, the patient can be covered with blankets [40].

Conclusion

In conclusion, the diagnosis of Myxedema coma is often challenging due to the various potential causes, and the symptoms can be challenging to detect, particularly in elderly patients with a history of heart disease. However, early diagnosis is crucial, typically through clinical symptoms and serum TSH, to initiate immediate treatment with thyroid hormone. The presented cases demonstrated successful treatment of Myxedema coma using levothyroxine and glucocorticoids. Nevertheless, outpatient follow-ups are necessary to assess the prognosis of AIM and monitor the patient's recovery. Therefore, prompt recognition and management of Myxedema coma are essential to prevent potential life-threatening complications and improve patient outcomes.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors have no conflicts of interest to disclose.

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Authors Contributions

All authors made a significant contribution to the work reported and took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Figures

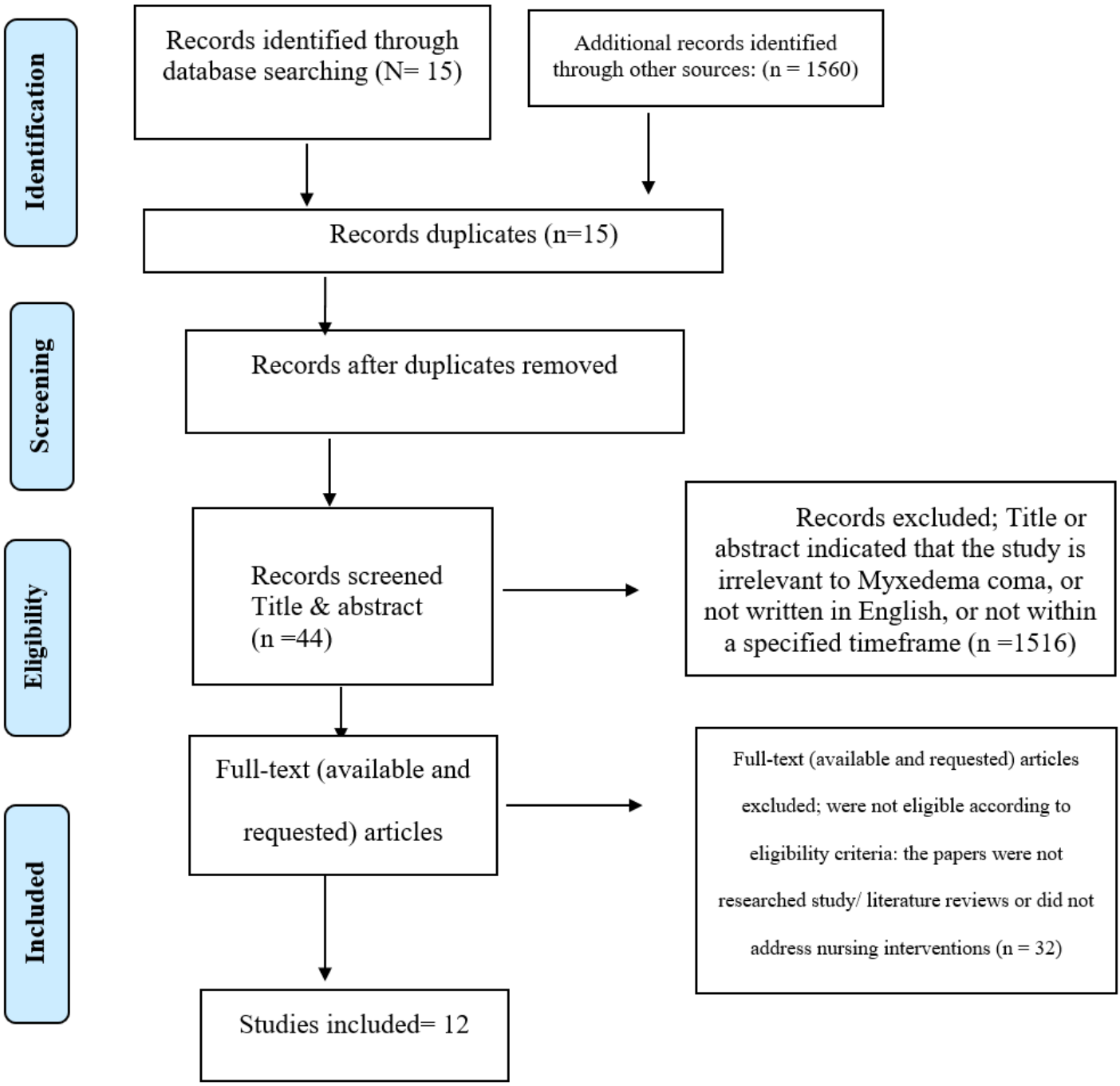

Figure 1

PRISMA flowchart