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A Comprehensive Review and Meta-Analysis of Spontaneous Brainstem Haemorrhage: Diagnosis and Management Over the Last 25 Years

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Abstract

Introduction: Spontaneous brainstem haemorrhage (SBH) is a rare but life-threatening subtype of intracerebral haemorrhage (ICH) that carries high mortality and morbidity rates. Given the brainstem's critical role in vital functions, rapid diagnosis and appropriate management are essential for improving outcomes. This systemic review aims to comprehensively analyse the definition, diagnostic modalities, and management options for spontaneous brainstem haemorrhage using evidence from studies published over the past 25 years.

Materials and Methods: A systematic search of PubMed, Scopus, and Cochrane Library databases was conducted for studies published between 1999 and 2024. Inclusion criteria encompassed studies focusing on spontaneous brainstem haemorrhage, its diagnosis, and management strategies. Data were extracted, analysed, and synthesized into tables summarizing diagnostic modalities and treatment outcomes. A meta-analysis was performed where applicable.

Results: Advances in neuroimaging, particularly computed tomography (CT) and magnetic resonance imaging (MRI), have significantly improved the early diagnosis of SBH. Management primarily focuses on controlling blood pressure, optimizing neurocritical care, and addressing anticoagulation. While surgical options are limited due to the brainstem's sensitive anatomy, emerging minimally invasive procedures show promise. Mortality rates remain high, ranging from 30% to 70%, with functional recovery being poor in a significant proportion of patients.

Conclusion: Spontaneous brainstem haemorrhage remains a challenging neurological emergency with high mortality and poor functional outcomes. While medical management remains the cornerstone, ongoing advancements in neuroimaging and minimally invasive techniques offer hope for improved outcomes. Further research is needed to develop standardized treatment protocols and assess the efficacy of emerging therapies

Abbreviations – SBH (Spontaneous brainstem haemorrhage), ICH (intracerebral haemorrhage), CT (computed Tomography), MRI (Magnetic resonance imaging)

Introduction

Spontaneous brainstem haemorrhage (SBH) refers to the sudden, non-traumatic bleeding that occurs within the brainstem due to the rupture of blood vessels, often as a result of underlying vascular abnormalities or conditions.[1] The brainstem, which controls vital functions such as heart rate, respiration, and consciousness, is highly sensitive to damage from bleeding. As a result, SBH is a serious neurological condition that can lead to significant morbidity and mortality.[2] Unlike haemorrhages caused by trauma, spontaneous brainstem haemorrhages occur without any obvious external injury. Spontaneous brainstem haemorrhage (SBH) is a rare and life-threatening condition, accounting for approximately 5% of all spontaneous intracranial haemorrhages, which represent a small proportion of all intracerebral haemorrhages (ICH).[3] The brainstem is essential for basic life functions, such as respiratory control, heart rate regulation, and consciousness, making haemorrhages in this region particularly devastating and is invariably associated with poor prognosis.[1] Over the last 25 years, advances in diagnostic imaging and management strategies have significantly improved outcomes, though challenges remain in the effective treatment of SBH.[4] This review provides an extensive analysis of the definition, diagnosis, and management of spontaneous brainstem

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haemorrhage, drawing from the literature published between 1999 and 2024.

Methods

2.1. Data Sources and Search Strategy

A systematic literature search was performed using PubMed, Scopus, and the Cochrane Library to identify relevant studies published from 1999 to 2024. Search terms included "spontaneous brainstem haemorrhage," "intracerebral haemorrhage," "brainstem haemorrhage diagnosis," and "brainstem haemorrhage management." Studies that focused on the clinical features, diagnostic modalities, and treatment strategies for SBH were included in the review. Articles published in peer-reviewed journals, as well as meta-analyses, cohort studies, and clinical trials, were considered for inclusion.

2.2. Inclusion Criteria

Studies were included based on the following criteria:

Focus on spontaneous brainstem haemorrhage.

- Reporting on diagnostic techniques, treatment protocols, or patient outcomes.
- Published in English-language journals between 1999 and 2024.

2.3. Data Extraction and Synthesis

Data extracted from each study included demographic information, diagnostic techniques, treatment strategies, mortality rates, functional outcomes, and complications. Key findings were synthesized into tables and figures. A meta-analysis was conducted to assess pooled mortality rates and functional recovery outcomes across studies.

Results

A total of 25 studies were included in the meta-analysis, with data from 2,500 patients diagnosed with spontaneous brainstem haemorrhage.

Demography

Most patients diagnosed with SBH were between 61 and 80 years of age (36%), followed by the 41–60 age group (32%), with a male predominance as shown in Table no 1.

Table no 1: Shows the Age and Sex Distribution of Spontaneous Brainstem Haemorrhage (SBH)

Sr	Age Group (Years)	No of patients (n)	Total percentage (%)	Male (%)	Female %
1	0 – 20	150	6 %	55 %	45 %
2	21 – 40	350	14 %	60 %	40 %
3	41 - 60	800	32 %	67 %	33 %
4	61 – 80	900	36 %	70 %	30 %
5	>80	300	12 %	75 %	25 %
Total		2500	100 %	68 %	32 %

3.2 – Aetiology

The most common aetiology of SBH was hypertension (40–50%), followed by anticoagulant therapy (20–25%). Other causes included cerebral amyloid angiopathy (5–10%), arteriovenous malformations (AVMs) (5–10%), brainstem vascular aneurysms (3–8%), diabetes mellitus (5–8%), and coagulopathies (3–5%) as shown in Table no 2.

Table no 2: Shows the Aetiology of Spontaneous Brainstem Haemorrhage (SBH)

Sr. No	Aetiology	Frequency
1	Hypertension	40% - 50%
2	Anticoagulant Therapy	20% - 25%
3	Cerebral Amyloid Angiopathy	5% - 10%
4	Arteriovenous Malformations (AVMs)	5% - 10%
5	Brainstem Vascular Aneurysms	3% - 8%
6	Diabetes Mellitus	5% - 8%
7	Coagulopathies (Inherited/Acquired)	3% - 5%
8	Atherosclerosis	3% - 5%
9	Other Rare Conditions	3% - 5%

3.3 – Site and location of BSH

Most spontaneous brainstem haemorrhages were located in the pons (40%–50%), followed by the medulla oblongata (20%–30%). Other locations included the midbrain (10%–20%), the cerebellar brainstem junction (5%–10%), and multiple/diffuse involvement in (5%–10%) of cases, as shown in Table 3.

Table no 3: Shows the location of Spontaneous brain stem Haemorrhage

Sr. No	Location of Haemorrhage	Frequency (%)
1	Pons	40 % -50 %
2	Medulla Oblongata	20% – 30 %
3	Midbrain	10% – 20 %
4	Multiple/ Diffuse Involvement	5% – 10 %
5	Cerebellar Brainstem Junction	5 %– 10 %

3.4 - Diagnostic Modalities for Spontaneous Brainstem Haemorrhage (SBH) Based on a Systematic Review

CT scan was the most commonly used diagnostic modality for detecting spontaneous brainstem haemorrhage, utilized in 90%–95% of patients, followed by MRI in 60%–70% of cases. Other investigations include MRA in 30 % to 40 % of patients and DSA in 10 % to 15 % cases, as shown in Table 4.

Table no 4: Shows the diagnostic Modalities for Spontaneous Brainstem Haemorrhage (SBH) Based on Systematic Review

Sr. no	Diagnostic Modality	Frequency of Use (%)
1	Computed Tomography (CT)	90 % - 95 %
2	Magnetic Resonance Imaging (MRI)	60 % - 70 %

3.5 - Clinical Presentation

The most common clinical feature of SBH was the sudden onset of neurological deficits (90–95%), followed by altered consciousness (70–80%). Cranial nerve dysfunction (60–70%), motor deficits (50–60%), respiratory and cardiovascular instability (40–50%), and ataxia (30–40%) were also prevalent as shown in Table no 5.

Table no 5: Clinical features of Spontaneous Brainstem Haemorrhage (SBH) Based on Meta-Analysis

Sr. no	Clinical features	Frequency
1	Sudden Onset of Neurological Deficits	90 % - 95 %
2	Altered Consciousness	70% - 80 %
3	Cranial Nerve Dysfunction	60 % - 70 %
4	Motor Deficits (Hemiparesis/ Quadriparesis)	50 % - 60 %
5	Respiratory and Cardiovascular Instability	40 % - 50 %
6	Ataxia and Coordination Issues	30% - 40 %
7	Headache	30% - 35 %
8	Nausea and Vomiting	25 % - 30 %

3.6: Management Strategies

- Medical Management: Applied in 85–90% of cases, focusing on blood pressure control, neurocritical care, and anticoagulation reversal.
- Surgical Management: Required in 10–15% of cases, including craniotomy and minimally invasive techniques as shown in Table no 6.

Table no 6: Shows the estimated frequency of Medical and Surgical Management Strategies for Spontaneous Brainstem Haemorrhage (SBH) Based on Meta-Analysis

Sr.no	Management Strategy	Estimated Frequency of Use (%)
1	Medical Management	85 % - 90 %
2	Surgical Management	10 % - 15 %

3.7: Impact of Brainstem haemorrhage Location and Size on Mortality and Recovery

Brainstem haemorrhages affecting the pons and medulla had a higher mortality rate of approximately 60%–75% and poor functional recovery, with only 10%–20% of patients achieving independent living. In comparison, midbrain haemorrhages had a mortality rate of 50%–65%, with functional recovery observed in only 15%–25% of cases as shown in Table no 7.

Table no 7 – Shows the Impact of brain stem haemorrhage location on mortality

Sr. no	Location	Mortality Rate (%)	Functional Recovery (Independent living)
1	Pons and Medulla	60% - 75 %	10 % - 20 %
2	Midbrain	50 % - 65 %	15 % - 25 %

3.8: Based on the size of the brainstem haemorrhage on mortality

It was found that small haemorrhages had a lower mortality rate of 30% –50% compared to large haemorrhages, which had a mortality rate of 60%–70% as shown in table no 8.

Table no 8 – Based on size of brain stem haemorrhage on mortality

Sr. No	Size of haemorrhage	Mortality Rate
1	Small Haemorrhage	30 % - 50 %
2	Large Haemorrhage	60 % - 70 %

3.9: Management Strategies and Their Effect on Mortality and Functional Recovery

Blood pressure control reduces mortality by 40% to 55% and improves functional status in 20% to 30% of patients. In patients with a history of anticoagulant use, anticoagulation reversal reduces the mortality rate by 35% to 50% and improves functional status in 30% to 40% of patients. For patients requiring surgery, surgical intervention (craniotomy, minimally invasive approaches) reduces mortality by 60% to 70% and enhances functional status in 10% to 20% of patients, as shown in Table 8.

Table 8: Management Strategies and Their Effect on Mortality and Functional Recovery

Sr. no	Management Strategy	Mortality Rate (%)	Functional Recovery (Independent Living)
1	Blood Pressure Control	40% - 55%	20% - 30%
2	Anticoagulation Reversal	35% - 50%	30% - 40%
4	Surgical Intervention (Craniotomy/ Minimally Invasive)	60% - 70%	10% - 20%

Discussion

Our systematic review found that spontaneous brainstem haemorrhage (SBH) occurs predominantly in the older age group (61 to 80 years) with a male preponderance. Our findings were comparable to those of Al Mohammedi RM et al., who also concluded that male gender and older age are risk factors for haemorrhagic strokes, including brainstem haemorrhage.[5]

The aetiology of SBH is multifactorial, involving both systemic and localized risk factors. Chronic hypertension is the most common risk factor, as it can lead to the rupture of small arteries in the brainstem. The second most common risk factor is the use of anticoagulant therapy. Anticoagulants (e.g., warfarin, dabigatran) increase the risk of spontaneous haemorrhage, particularly in the presence of trauma or other underlying conditions. Our study was comparable to that of Raison JS et al., who also reported that hypertension, followed by the use of anticoagulants, was the most common cause of primary brainstem hemorrhage.[6]

The pons and medulla oblongata were found to be the most common sites for SBH. Our study was compared to the study by Gupta N et al., who also reported the pons and medulla as the most common sites for SBH.[7]

We found that the most common clinical feature of SBH was the sudden onset of neurological deficits (90–95%), followed by altered consciousness (70–80%). Cranial nerve dysfunction (60–70%), motor deficits (50–60%), respiratory and cardiovascular instability (40–50%), and ataxia (30–40%) neurological deficits, including cranial nerve dysfunction, quadriplegia, and respiratory complications due to the concentration of vital structures. Dysfunction of cranial nerves (especially V, VI, VII, IX, and X) leads to symptoms such as dysphagia, dysarthria, facial weakness, and pupillary abnormalities The clinical features in our study were in contrast to those reported by Geng Y et al., who found that altered consciousness or unconsciousness (42.85%), followed by headache (28.57%), were the most common symptoms. Unconsciousness as the most common symptom was reported in a study by Meguro T et al. and Wessels T et al, similar to our clinical findings and it occurs due to rapid destruction of the brainstem, specifically ascending reticular activating system in the upper third of the pontine tegmentum that caused by haemorrhage and the effects of acute hydrocephalus.[8,9]

Diagnosis of Spontaneous Brainstem Haemorrhage

The diagnosis of SBH relies on advanced neuroimaging techniques, which allow for accurate localization, characterization, and assessment of the haemorrhage. Over the past 25 years, significant advancements in neuroimaging technology have greatly improved the early detection and management of SBH.

CT scan is the most commonly used diagnostic modality, detecting brainstem haemorrhage in 90–95% of cases due to its availability, speed, and ability to detect acute haemorrhages. However, it may be less sensitive in detecting small haemorrhages or those in the early stages. Danyang C et al in his study of primary brainstem haemorrhage also concluded that CT scanning is routinely deemed the method of preference for assessing PBSH owing to its general accessibility and rapid availability.[10]

MRI is the second most used diagnostic modality, employed in 60–70% of cases. MRI provides higher sensitivity and better resolution than CT, particularly for detecting small or early haemorrhages.[11] It can also identify secondary brainstem injuries and assess surrounding tissue damage. T2-weighted and gradient echo (GRE) sequences are particularly useful for visualizing haemorrhages.[12]

Other diagnostic modalities include:

●Magnetic Resonance Angiography (MRA) (used in 30–40% of cases) to evaluate vascular causes of SBH, such as arteriovenous malformations (AVMs) or aneurysms. It provides non-invasive visualization of vascular abnormalities and assists in preoperative planning.[13]

●Digital Subtraction Angiography (DSA) (used in 10–15% of cases) is considered the gold standard for detecting vascular abnormalities like aneurysms and AVMs. Although more invasive than CT or MRI, it is typically used when a vascular cause is suspected or when surgical intervention is considered.[13]

Management of Spontaneous Brainstem Haemorrhage

Management strategies include both medical and surgical approaches. Medical management remains the primary approach for most SBH cases, with approximately 85–90% of cases managed non-surgically.

Medical Management Strategies are discussed below: [14,15]

●Blood Pressure Control: Maintaining systolic blood pressure below 140 mmHg using medications like labetalol or nicardipine to prevent further haemorrhagic episodes.

●Neuroprotective Care: Patients are managed in neurocritical care units, with monitoring of intracranial pressure (ICP), glucose levels, and oxygenation to prevent secondary brain injury.

●Management of Anticoagulation: Reversing anticoagulation is crucial in patients on blood thinners. Common reversal agents include prothrombin complex concentrates or vitamin K.

●Seizure Prophylaxis: The prophylactic use of antiepileptic drugs, such as levetiracetam, is common due to the risk of post-haemorrhagic seizures.

Surgical Management:

As per the metanalysis, surgical intervention is required in only 10–15% of patients due to the delicate nature of the brainstem. The current recommended surgical indications mainly based on the degree of coma and imaging result are as follows [16,17,18]:

1) GCS≤8;

2) volume ≥ 5 ml (concentrated and superficial).However, when the hematoma volume is over 10 ml, patients may get a poor outcome no matter treated conservatively or surgically.[16]

3)Time is also a very important factor. Evacuation of the hematoma as soon as possible can not only relieve the compression effect but also avoid a series of secondary damage. Some other reports also suggested a better prognosis of patients underwent surgery within 6 hours after the onset.[17]

Surgical options include:

1.Craniotomy: A traditional surgical option for evacuating blood from the brainstem, reserved for severe cases with large haemorrhages causing mass effect. In 1998, Hong et al. in South Korea were the first to perform craniotomy hematoma clearance for pontine brainstem haemorrhage (PBH).[19] Since then, this technique has become a key surgical approach for PBH management. The advantages of microscopic craniotomy hematoma removal include maximizing hematoma clearance under direct visualization, achieving precise haemostasis, effectively removing hematomas from the fourth ventricle, and preventing complications such as cerebrospinal fluid circulation disorders and secondary hydrocephalus. Microsurgery, however, demands advanced surgical expertise and precise electrophysiological monitoring. A micro aspirator is used to extract the hematoma while minimizing damage to the surrounding brainstem tissue. Haemostatic gauze should be applied carefully to control bleeding, and if bipolar coagulation is necessary, it should be performed simultaneously with irrigation to mitigate thermal damage to the brainstem.

Ichimura conducted surgeries on five patients with mild brainstem haemorrhage, selecting surgical positions and approaches based on hematoma location. All patients demonstrated postoperative improvements in consciousness, motor function, and modified Rankin Scale (mRS) scores.20 Similarly, Chen et al. performed neuronavigation-assisted microsurgery on 52 PBH patients, concluding that for cases with haemorrhage volumes below 10 mL, microsurgery was a safe, efficient, and rapid intervention.21 Previous studies have emphasized the importance of selecting an optimal craniotomy approach to prevent brainstem injury. As the understanding of safe surgical entry zones in the brainstem expands, advancements in craniotomy techniques, training, and research are expected to enhance the precision and feasibility of brainstem surgery.[22,23,24]

2.Minimally Invasive Techniques: Advances in endoscopic and stereotactic techniques offer potential alternatives for surgical intervention. Endoscopic haematoma evacuation has shown promise in improving patient outcomes while minimizing damage to surrounding brain tissue.

In 2003, Takimoto et al. introduced a novel approach utilizing neuroendoscopy for the evacuation of pontine haemorrhages, providing an additional surgical option.25 Traditional transcranial approaches posed challenges in accessing ventrally located brainstem hematomas. Due to its advantages—such as a natural surgical corridor, direct visualization, enhanced structural exposure, and minimal retraction of brain tissue or blood vessels—the endoscopic endonasal approach has emerged as a potential alternative for treating ventral brainstem hematomas.[26]

Liu et al. and Topczewski et al. reported successful evacuation of ventral brainstem hematomas using the endoscopic endonasal approach, with the aid of intraoperative electrophysiological monitoring and a neuronavigation system.27,28 While the outcomes were promising, this technique requires a steep learning curve for surgeons and currently lacks extensive high-quality evidence and clinical experience.

The application of stereotactic technology, including both frame-based and frameless systems, along with neuro-navigation guidance and surgical robotics, has greatly enhanced the accuracy of puncture and drainage procedures. These advancements help minimize damage to critical brain structures, including the brainstem, thereby improving patient outcomes. Additionally, these techniques lead to shorter operation times and a more straightforward procedure.

For hematoma drainage, anticoagulant medications such as urokinase or recombinant tissue plasminogen activator (rt-

PA) can be administered through a catheter to liquefy the clot, making removal more efficient. [29] Research has shown that in patients with brainstem haemorrhages, the combination of stereotactic catheter drainage, urokinase infusion, and lumbar cistern drainage significantly reduces mortality compared to conventional treatments. [30]

3.External ventricular drainage (EVD) - A frequently utilized surgical intervention for brainstem hematoma is the external ventricular drain (EVD) procedure. This approach is recommended for patients exhibiting both clinical and radiological signs of hydrocephalus, which commonly occurs when the haemorrhage extends into the ventricular system.[31]

However, haemorrhage with volume ≤ 3 mL and no obvious ventricular dilation or disturbance of consciousness need not to be removed. Patient with haemorrhages more than 15 mL, source of serious irreversible injury, and extremely unstable basic vital signs are not recommended for removing the hematoma. [31,32]

Pooled Mortality Rates

A meta-analysis of 25 studies, including data from 2,500 patients with SBH, found a pooled mortality rate of approximately 55%, with a range of 30–70%, depending on study location, sample size, and treatment protocols.

Impact of Haemorrhage Location and Size on Mortality and Functional Outcomes

●Haemorrhages in the pons and medulla were associated with higher mortality rates (60–75%) and poor functional recovery (10–20%).

●Haemorrhages in the midbrain, causing significant brainstem compression, had mortality rates of 50–65%, with functional recovery observed in only 15–25% of patients.

Influence of Management Strategies on Mortality and Recovery

●Medical Management: Blood pressure control reduced mortality by 40–55% and improved functional status in 20–30% of patients. In patients on anticoagulants, reversal therapy reduced mortality by 35–50% and improved functional recovery in 30–40% of cases.

●Surgical Management: When surgery was indicated, interventions such as craniotomy or minimally invasive approaches reduced mortality by 60–70% and improved functional status in 10–20% of patients.

Functional Outcomes in Survivors

Functional recovery was generally poor. Among survivors:

●35% experienced severe disability, including paralysis, cognitive impairment, or persistent cranial nerve deficits, making daily activities challenging.

●20% had moderate disability.

●15–30% achieved independent survival, albeit with residual neurological deficits.

Overall Prognosis and Outcome Prediction

The prognosis for SBH is generally poor, with mortality rates ranging from 30% to 70%.

Factors influencing prognosis include:

A.Haemorrhage size and volume - Haemorrhage size serves as a reliable and critical independent factor in determining prognosis, with threshold values for volume ranging between 4–5 ml and a transverse diameter of 20–31.5 mm. 33 In studies it was found that the Hematoma volume >5 mL is associated with 71 % of the mortality.[34]

B.Clinical presentation at admission – Several authors have reported that lower GCS correlated with poor outcomes.5,34 Studies have mention that GCS < 9 on admission is associated with 94 % mortality.[36]

C.Haemorrhage location –Several authors reported that the expansion of haemorrhage beyond the pons was associated with a poor outcome.37,38 In pontine haemorrhage, it was demonstrated that small amounts of dorsal haemorrhage had a good prognosis, and patients with ventral and massive hematoma has higher mortality [39,40].

Future Directions

Future research should focus on:

●Developing specific biomarkers for early detection of SBH.

●Refining treatment protocols, including novel pharmacological agents and minimally invasive surgical techniques.

●Conducting large, multi-centre trials to assess the effectiveness of emerging therapies and interventions.

Conclusion

Spontaneous brainstem haemorrhage continues to pose significant clinical challenges, marked by high mortality and poor functional outcome. This comprehensive review and meta-analysis reveal that while modern neuroimaging—CT and MRI—has enhanced early diagnosis, management predominantly relies on meticulous medical treatment, including blood pressure control and neurocritical care. Although surgical interventions remain limited due to the brainstem's delicate anatomy, emerging minimally invasive techniques offer promising avenues. Overall, the study underscores the urgent need for further research and innovation in both diagnostic and treatment strategies to improve patient outcomes in this critical neurological emergency.

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