Real-World Evidence – The Clinical Burden of Spinal Muscular Atrophy (SMA) in Abu Dhabi, UAE.

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1. Scientific Abstract

Background*:* SMA is a rare disease that occurs in approximately 1 in 10,000 live births worldwide and is one of the most common causes of infant mortality. Due to the lack of available data on the clinical impact of SMA in the UAE, and the emergence of new SMA treatments, it became necessary to evaluate the burden of SMA in Abu Dhabi. ***Methods****:* A retrospective review was conducted on Malaffi EHRs to analyse SMA patients, who were classified into two cohorts: (1) those with SMA1 and (2) those with other types of SMA (including SMA2, SMA3, and SMA4). ***Results***: In 2021, the occurrence of SMA in Abu Dhabi was estimated to be 1 in 12,290 individuals. The average age at the time of diagnosis for SMA1 patients was 6 months (min: 19 days – max: 11 months), while for other types of SMA, it was 17 years (min: 2 months – max: 97 years). SMA patients were predominantly male (57%) and Emirati (62%). Diagnostic techniques for SMA were unclear, with muscle biopsy being the only recorded test for 1 out of 150 SMA patients. Paediatricians were identified as the clinical specialty most actively involved in managing the condition. The most frequently reported SMA-related symptoms were scoliosis (n=598, total encounters), muscle weakness (n=578), failure to thrive (n=484), feeding difficulties (n=465), dysphagia (n=337), and dehydration (n=195). Whereas the most commonly reported SMA-related co-morbidities were GERDs (n=639), hypertension (n=195, total encounters), and pneumonia (n=130). The most frequently reported SMA-related services were dietary counselling and surveillance (23%), tracheostomy (20%), and dependence on respiratory support (20%). Regarding treatments, more SMA medications were prescribed for patients (n=28 pts) than were dispensed (n=13 pts), with risdiplam being the most prescribed (n=18 pts) and only dispensed treatment (n=13 pts). The secondary analysis identified that the average time to diagnosis was 32 ± 32 days for SMA1 patients (n=6 pts) and 139 ± 239 days for other SMA types (n=73 pts). Several endpoints related to treatment could not be determined due to incomplete/ missing data, including diagnosis-to-treatment ratio, and time-to-treatment. In addition, the mortality rate and the

occurrence of prenatal diagnoses could not be elucidated. ***Summary***: SMA is a heterogenous and progressive disease that requires continuous support and monitoring from healthcare professionals, including medicinal treatment, physical therapies, and other SMA-related supportive and life-prolonging services. Further, in severe cases (i.e., SMA1) onset occurs within the first 6 months of life, meaning that affected individuals will experience the burden of SMA for most of their life. All things considered, the clinical burden of SMA in Abu Dhabi is significant, as reported worldwide.

2. Background

Spinal muscular atrophy (SMA) is a rare disease that occurs in approximately 1 in 10,000 live births and is one of the most common causes of infant mortality[1, 2]. SMA is an autosomal recessive genetic disorder that worsens over time[3]. It can be caused by homozygous deletions in the survival motor neuron-1 (SMN1) gene, which account for 95% of cases, or by single point mutations and heterozygous deletions in SMN1, which account for 5% of cases[4]. The SMN1 gene encodes the SMN protein, which plays a pivotal role in motor function. Importantly, reduced SMN levels leads to progressive muscle denervation, atrophy and eventually total loss of motor function (paralysis)[3, 5]. Muscle atrophy can also lead to disease-related co-morbidities such as, but not limited to; dyspnea and respiratory anomalies, feeding difficulties, acute respiratory failure, dysphagia, failure to thrive, muscle weakness, and scoliosis. These co-morbidities result in patient utilisation of healthcare services such as, but not limited to, mechanical ventilation (and associated tracheostomy), nutritional support (and associated gastrostomy), physical therapy, occupational therapy, speech therapy, sleep studies, and orthopaedic surgery[6]. As such, SMA carries significant clinical burden for patients and healthcare systems.

The clinical burden of SMA is strongly associated with SMA type. Five types of SMA have been characterized, types 0 to 4[2, 7]. Type 0 (also known as prenatal SMA) is associated with patient death typically in utero or within one week of delivery. Type 1 (SMA1, also known as Werdnig Hoffman Disease) presents between 0-6 months of age and is the most common SMA type (~50–60% of all SMA cases)[8, 9]. Prior to the advent of therapeutic treatments, SMA1 patients' life expectancy typically did not extend beyond 2 years[3]. Type 2 (SMA2, also called Dubowitz disease) patients present with muscle weakness typically between 7-18 months of age. These patients usually achieve the 'sitting' milestone, but are never able to walk[3]. Type 3 (SMA3, also known as s Kugelberg Welander Disease) presents after 18 months of age in individuals who have achieved the 'walking' milestone. Finally, type 4 (SMA4) typically presents after 21 years of age. Compared with prenatal SMA and SMA1, SMA2, SMA3, and SMA4 are characteristically less severe and are associated with better prognostic outcomes[8, 10].

Until recently, SMA treatment relied on supportive care of the disease symptoms due to the paucity of therapeutic options. However, to date three SMA treatments are available, and all have been approved for clinical use by the United Arab Emirates (UAE) Ministry of Health and Prevention (MOHAP). These treatments work by increasing SMN levels in the body. Approved treatments include nusinersen (Spinraza®), onasemnogene abeparvovec-xioi (Zolgensma®), and risdiplam (Evrysdi®)[11-16]. Interestingly, a recent survey conducted in Europe revealed that 73% of SMA patients who wanted to initiate treatment could not, and this was primarily due to a lack of treatment access[17].

Since the advent of novel therapeutic treatments, and the availability of these treatments in Abu Dhabi, there is a need to identify the burden of SMA. Retrospective real-world analysis is used to identify the clinical burden of SMA in Abu Dhabi, an issue which is yet to be elucidated.

3. Methods

Objective & Endpoints

The objective of this report was to characterise the clinical burden of SMA by evaluating the following:

- Identify the number of patients diagnosed with:
    a. SMA1
    b. Other types of SMA (SMA2, SMA3, and SMA4)
- Identify if diagnosis was prenatal (type 0) or postnatal (types 1,2,3, and 4)
- Identify SMA patient demographics:
    a. Age at index date
    b. Age at final diagnosis
    c. Age at data analysis
    d. Weight at birth
    e. Sex
    f. Nationality
    g. Mortality rate
- Identify the SMA diagnostic pathway:
    a. Diagnostic techniques
    b. SMA involved clinician specialities
    c. Time to diagnosis
- Identification and frequency count of SMA-related symptoms
- Identification and frequency count of SMA-related co-morbidities
- Identification and frequency count of SMA-related services
- Characterise the SMA treatment paradigm:
    a. Frequency count of each SMA medication used:
        i. Nusinersen (Spinraza)
        ii. Onasemnogene abeparvovec-xioi (Zolgensma)
        iii. Risdiplam (Evrysdi)
            1. Number of prescribed SMA medications
            2. Number of dispensed SMA medications
            3. Diagnosis-to-treatment ratio
            4. Time-to-treatment

Study Design and Population

A retrospective review of Malaffi electronic health records (EHRs) and the Abu Dhabi death registry were used to characterise the clinical burden of SMA in Abu Dhabi. Patients were classified into two cohorts based on the International Classification of Diseases, Tenth Revision (ICD-10) code;

1. SMA1 = including G12.0, and

2. Other SMA types (encompassing SMA2, SMA3, and SMA4) = including G12.0 outliers, G12.1, G12.8, and G12.9.

This retrospective review of Malaffi EHRs was conducted in compliance with all relevant laws and regulations, and patient consent was waived. The data were de-identified to protect patient privacy and confidentiality. This project was reviewed by governing regulatory authority and approval was granted on 21st September 2022.

Sample Selection

This retrospective analysis included patients were who met the following criteria: a diagnosis of SMA as defined by at least one ICD-10 code to include G12.0, G12.1, G12.8, or G12.9, recorded in the Malaffi database between 1st January 2021 – 21st September 2022, and ≥1 year of medical history data recorded in the Malaffi database. Patients were considered as 'SMA1 outliers' if they were first diagnosed with SMA1 (G12.0) aged >1 years. These patients were considerd under 'other SMA types', rather than SMA1. No further restrictions related to the inclusion of participants' data were enforced.

Data Sources

The Malaffi database and the Abu Dhabi death registry were used to conduct this retrospective study, with data covering the study period. The Malaffi database is a longitudinal patient health information platform, which connects public and private healthcare providers. Malaffi is a public private partnership between the Department of Health (DOH) Abu Dhabi and Injazat. Malaffi captures all clinical data for patients residing in the emirate of Abu Dhabi, as well as all medical interactions including routine checkup, consultation or emergency treatment. The DOH Abu Dhabi granted IROS data access permissions to conduct de-identified data anlysis.

Data Analysis

Patient characteristics and study outcomes are summarised using descriptive statistics. Continuous variables are reported as mean, standard deviation and minimum and maximum values were appropriate. Categorical variables are presented as frequency counts and percentages. For this data analysis, ICD-10 and CPT4 codes are used to identify the relevant data.

Primary Analysis

Data analysis included all patients who were diagnosed with SMA and had a corresponding diagnostic code, including G12.0, G12.1, G12.8, or G12.9, recorded between 1st January 2021 and 21st September 2022.

The following data was analysed for this group:

- Patient demographics
- SMA diagnosis (SMA1 or other SMA types)
- Time period of SMA diagnosis (prenatal or postnatal)
- SMA involved clinician specialities
- SMA diagnostic techniques
- SMA-related symptoms
- SMA-related co-morbidities
- SMA-related services
- SMA treatment paradigm

Secondary Analysis

A secondary data analysis was performed, focusing on new patients whose index date fell within the study period. SMA1 patients who were aged ≥1 year at index date were reported as 'G12.0 outliers' and analysed under 'other SMA types'.

The following data was analysed for this group:

- New cases of SMA (SMA1 or other SMA types)
- Time to diagnosis
- Diagnosis-to-treatment ratio
- Time-to-treatment

Exploratory Analysis

- Re-classification of SMA type (SMA1, SMA2, SMA3, and SMA4) based on age at diagnosis.

4. Results

Population & Demographic Information

A total of 150 patients with SMA were identified in the Malaffi database between January 1st 2021 and September 21st 2022, 12 SMA1 patients and 138 patients with other types of SMA. (Appendix 1: Demographic Table). The identified SMA patients were majority male (57% of total pts.) and Emirati (62%).

In 2021, the prevalence of SMA was estimated at 1 in 12,290 individuals in Abu Dhabi. This calculation was based on the total population of approximately 1.51 million people residing in Abu Dhabi that year, and 123 recorded cases[18] (Appendix 2: Annual Diagnosis Counts).

A total of 79 patients were diagnosed with SMA for the first time (i.e., the index date) between January 1st 2021 and September 21st 2022, 6 SMA1 patients and 73 patients had other types of SMA (including SMA2, SMA3, and SMA4). The average age at index date for patients with SMA1 was 6 months (min: 19 days – max: 11 months), while for patients with other types of SMA it was 17 years (min: 2 months – max: 97 years). According to the information that is accessible, it seems that cases of SMA were solely diagnosed after birth, as there was no identification of prenatal diagnosis.

SMA1 patients had an average recorded age of death of 5 years (±4 years) and other SMA patients had an average recorded age of death of 41 years (±43 years). However, the mortality rate could not be confidently calculated due to the possible incomplete or inaccurate data. Our data suggests that only 5 individuals with SMA died during the study period, 3 SMA1 patients and 2 patients with other types of SMA. Overall, the average age at death was 19.4 years (min 2.4 months - max 71.9 years). In addition, data regarding birth weight was not available for new SMA patients who were born during the study period.

Age-based Estimated SMA Re-Classifications

The ICD-10 coding system provides information on SMA1 but does not distinguish between SMA2, SMA3 or SMA4 (see Appendix 6: Glossary for G12.1, G12.9 and G12.9 definitions). For this reason, an exploratory analysis was conducted to re-classify the population to SMA types according to their age at index date. The age buckets per SMA type were based on published estimates of SMA diagnosis ages. Results are

reported in Table 1 Estimates of Population SMA Types Based on Age at Index. The purpose of this analysis was to enhance comprehension of the dataset, though it was not used in the study findings as it does not correspond to the information recorded in the Malaffi EHRs.

Table 1 Estimates of Population SMA Types Based on Age at Index

Age at Index Date	**Inferred SMA type**	**Abbreviation**	**N**
Less than 6 months	Type 1	SMA1	18
6 months to 18 months	Type 2	SMA2	16
19 months to 20 years	Type 3	SMA3	74
19 months to 3 years	*Type 3a*	*SMA3a*	*15*
4 years to 20 years	*Type 3b*	*SMA34*	*59*
≥ 21 years	Type 4	SMA4	42
			Total: 150
Age-based classifications are based on those set forth by the National Institute of Health, UK[7]. Abbreviations: n = number, SMA = spinal muscular atrophy.			

SMA Diagnosis

Diagnostic Techniques

Both ICD-10 and CPT4 data were used to evaluate SMA diagnosis methods, however only 28% (n=42) of all patients (n=150) had ICD-10 data recorded, and CPT4 data was available for just 25% (n=37).

Diagnostic-related findings are reported in Table 2. Diagnostic Findings. The most reported diagnostic-related finding was related to abnormal levels of creatine kinase, which was recorded in 21% of patients, followed by genetic testing recorded in 11% of patients, MRI findings in 3% of patients, and EMG findings in <1% of patients. Findings related to muscle biopsy as a diagnostic tool were not reported. However, muscle biopsy was the only conducted diagnostic-related test identified from CPT4 code analysis. The performed diagnostic procedures/ tests are reported in Table 3. Diagnostic Procedures. Muscle biopsy was reported for only 1 patient, this patient was a G12.0 outlier (age-based classification estimate = SMA type 3b).

In general, there appears to be a mismatch between the available data for the diagnostic tests conducted and the recorded diagnoses derived from the results of those tests. As such, it was not possible to accurately determine the techniques utilised in diagnosing SMA.

Table 2. Diagnostic Findings

		SMA1	**Other SMA Types (SMA2, SMA3, SMA4)**					**Total**
Total no. of patients		**G12.0**	G12.0 outliers	G12.1	G12.8	G12.9	**Other SMA Types: Total**	
Total Population, n (%)		12 (8)	25 (17)	30 (20)	10 (7)	73 (49)	138 (92)	150 (100)
Population for which ICD-10 codes are available		5 (3)	6 (4)	4 (3)	3 (2)	24 (16)	37 (25)	42 (28)
Genetic testing		1 (20)	2 (33)	4 (100)	1 (33)	8 (33)	15 (41)	16 (38)
EMG		-	1 (17)	-	-	-	1 (3)	1 (2)
Biopsy*		-	-	-	-	-	-	-
Creatine kinase		4 (80)	6 (100)	1 (25)	1 (33)	20 (83)	28 (76)	32 (76)

MRI		-	1 (17)	-	1 (33)	2 (8)	4 (11)	4 (10)

Genetic related ICD-10 codes include: Z13.79, Q99.9, Q99.8, and Q93.5.
EMG related ICD-10 codes include: R94.131, R94.132, R94.133, R94.141, R94.142, R94.143, R94.8, and R94.9.
Creatine kinase related ICD-10 codes include: R74.8
MRI related ICD-10 codes include: R93.0, R93.8, R93.89, R93.9.
**No ICD-10 codes related to diagnosis that arose following muscle biopsy were identified (other than SMA diagnosis codes).*

Table 3. Diagnostic Procedures

		SMA1	**Other SMA Types (SMA2, SMA3, SMA4)**					**Total**
Total no. of patients		**G12.0**	*G12.0 outliers*	G12.1	G12.8	G12.9	**Other SMA Types: Total**	
Total Population, *n (%)*		12 (8)	*25 (17)*	30 (20)	10 (7)	73 (49)	138 (92)	150 (100)
Population for which CPT4 codes are available		6 (4)	*8 (5)*	4 (3)	3 (2)	16 (11)	31 (21)	37 (25)
Genetic testing		-	-	-	-	-	-	-
EMG		-	-	-	-	-	-	-
Biopsy		-	*1 (13)*	-	-	-	1 (3)	*1 (3)*
Creatine kinase		-	-	-	-	-	-	-
MRI		-	-	-	-	-	-	-
Nerve conduction studies		-	-	-	-	-	-	-

Genetic testing CPT4 codes include: 81479, 81406, 81405, 81404, 81401, 81400, 81337, 81336, and 81329.
EMG CPT4 codes include: 95864, 95863, 95861, and 95860.
Biopsy CPT4 codes include: 20250, 20240, 20225, 20220, 20206, 20205, and 20200.
Creatine kinase CPT4 codes include: 82550.
MRI CPT4 codes include: 72158, 72157, 72156, 72149, 72148, 72147, 72146, 72142, and 72141.
Nerve conduction studies CPT4 codes include: 95912, 95911, 95910, 95909, 95908, and 95907.

SMA Involved Clinician Specialities

Paediatricians were the most involved with SMA patients (40%), followed by internal medicine clinicians (17%), and orthopaedic surgeons (7%).

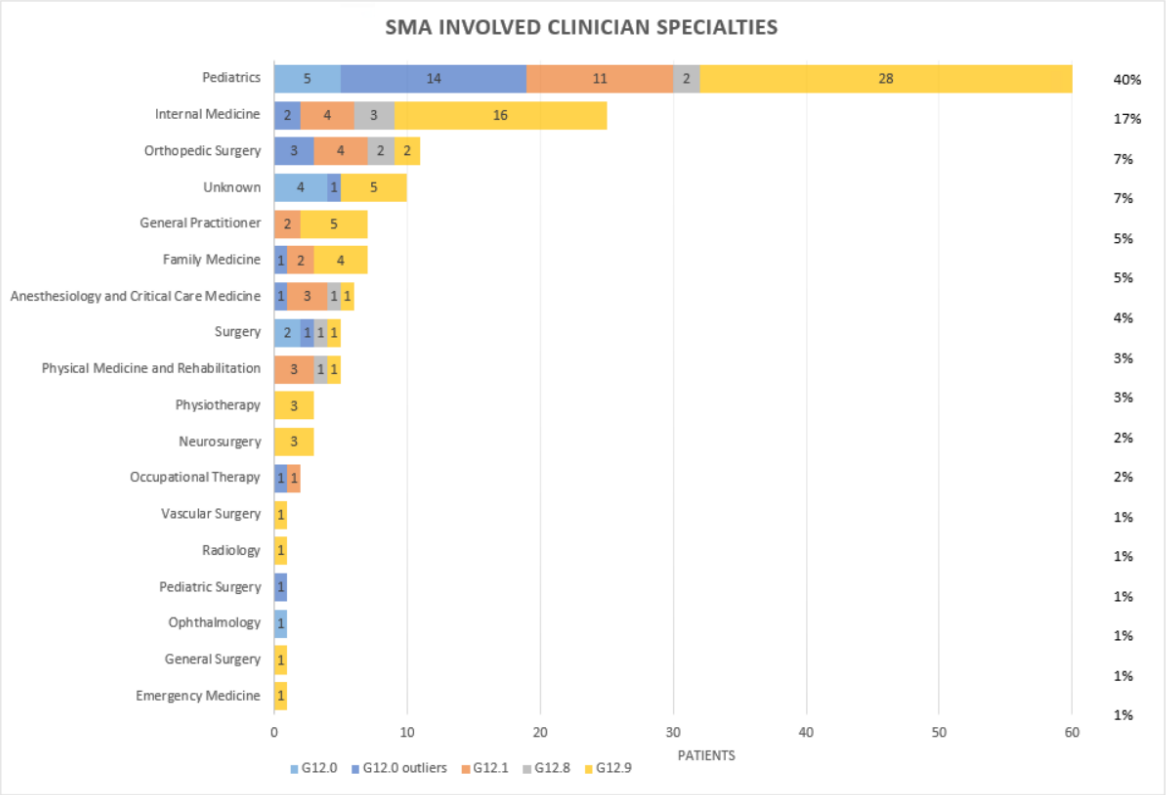

Figure 1. SMA Involved Clinical Specialities. The numbers displayed on the bar indicate the count of patients who have received a diagnosis of SMA. The percentages reflect the proportion of all SMA patients with their most recent SMA diagnosis code (i.e., G12.0, G12.1, G12.8, or G12.9).

Time to Diagnosis

Secondary analysis data demonstrates that the average time to diagnosis for SMA1 patients was 32 ± 32 days, calculated as the time between the first recorded SMA symptom and the index date. For other SMA types, the time to diagnosis was 139 ± 239 days (equivalent to approximately 4.5 months). Further, data revealed that 5 out of 6 patients newly diagnosed with SMA1 during the study period were diagnosed between 0-6 months of age (diagnosis window: 0 - 1 month = 1 pt., 1 - 6 months = 3 pts., 6 - 8 months = 1 pt., 8 - 10 months = 1 pt., 10-12 months = 0 pts.).

SMA-Related Symptoms

All recorded SMA-related symptoms are reported in Appendix 3: SMA-Related Symptoms. The most frequently reported clinical symptoms were scoliosis, unspecified (n=598, total encounters), muscle weakness (generalised) (n=578), failure to thrive (child) (n=484), feeding difficulties (n=465), dysphagia, unspecified (n=337), dehydration (n=195), other secondary scoliosis, thoracolumbar region (n=179), and respiratory failure, unspecified (n=114).

Developmental Milestones

Failure to thrive (child) was the most commonly recorded diagnosis related to developmental milestones (n=484, total encounters), followed by delayed milestone in childhood (n=436), lack of expected normal

physiological development in childhood (n=340), other lack of expected normal physiological development in childhood (n=9), short stature child (n=4) and adult failure to thrive (n=1) (Appendix 3: SMA-Related Symptoms). Data indicates that most developmental diagnoses are directed toward children, with only 1 record of an adult diagnosis.

SMA-Related Co-Morbidities

All recorded SMA-related comorbidities are reported in Appendix 4: SMA-Related Co-morbidities. The most frequently reported clinical comorbidities were gastro-oesophageal reflux disease without esophagitis (n=639), essential (primary) hypertension (n=195, total encounters), and pneumonia, unspecified organism (n=130).

SMA-Related Services

All recorded SMA-related services are reported in Appendix 5: SMA-Related Services. Both ICD-10 and CPT4 data were used to evaluate SMA-related services, though only 53% of all patients had ICD-10 data available, and CPT4 data was available for just 25% of all patients. The most reported SMA-related services were dietary counselling and surveillance (68% of pts. that had accessible ICD-10 code data), tracheostomy (58%), and dependence on respiratory [ventilator] (57%).

The most common related activities performed were intubation, endotracheal, emergency procedure (62% of pts. that had accessible CPT4 code data), change of gastrostomy tube, percutaneous without imaging or endoscopic guidance (49%), and laparoscopy surgical esophagogastric fluoroplastic (e.g., Nissen, Toupet procedures) (11%).

SMA Treatment (Medications)

Out of 150 patients, only 28 patients were prescribed SMA treatment (11 Emirati; 17 expatriates; 19% of the total pts), with risdiplam being the medication that was most frequently prescribed (n=18 pts). In addition, risdiplam was the only dispensed SMA treatment. However, there is a discrepancy between the number patients for whom risdiplam was prescribed (n=28 pts.) versus dispensed (n=13 pts.; 5 Emirati; 8 expatriates; 9% of the total pts.). Overall, data demonstrates that more SMA medications were prescribed for patients (n=28 pts.) than were dispensed (n=13 pts) during the study period.

Diagnosis-to-treatment ratio, and time-to-treatment could not be confidently calculated due to the discrepancy between the number of prescribed versus dispensed medications in the database. For example, nusinersen and onasemnogene abeparvovec-xioi were prescribed (8 units and 3 units respectively) but none were dispensed. The secondary analysis revealed 4 patients who were newly diagnosed with SMA and received treatment during the study period. Data suggests that the average time between their initial SMA diagnosis and the dispensing of the first SMA treatment was 271 days, with a minimum of 85 days and a maximum of 1.3 years.

5. Limitations & Recommendations

All research studies have limitations since it is impossible to design a study that perfectly captures every aspect of the subject being studied. It is important to discuss these limitations and consider the study findings with consideration for the noted limitations. Recommendations have been proposed to address each limitation.

Limitation 1: The gold standard diagnostic test for SMA is genetic testing, such as DNA sequencing or targeted mutation analysis of the SMN1 gene. However, it is unclear what diagnostic methods are used for SMA in Abu Dhabi as per the Malaffi dataset. Only 1 out of the 150 patients had documentation of undergoing a diagnostic test (muscle biopsy). The data suggests that genetic testing was not performed for all patients before a SMA diagnosis was made.

> ***Recommendation 1****: It is crucial to elucidate if either (a) there is missing data on diagnostic techniques, or (b) whether clinicians are following the latest advances in SMA diagnostic workups. Regardless of the scenario, it would be beneficial for clinicians to participate in clinical medical education courses on this topic to stay up to date on the latest SMA advancements in knowledge and best practice.*

Limitation 2: This study necessitates the use of EHRs to identify diagnoses, activities, and outcomes. However, it is recognised that such records may not always be precise, leading to potential data inaccuracies. For example, there may be instances of misclassification bias, where incorrect diagnosis codes were recorded due to human error, causing misclassification of the type of SMA and resulting in biased findings.

> ***Recommendation 2a:*** *It is necessary to update the EHR systems which feed into the Malaffi database to prevent medically implausible entries from being recorded. For example, the systems should be configured to disallow the first diagnosis of type 1 SMA (G12.0) in patients 1-years-old or above.*
>
> ***Recommendation 2b:*** *In conjunction with system updates to preclude the inclusion of medically implausible entries, it is crucial to provide physicians with SMA-specific continuing medical education courses. Such courses would enhance the precision of diagnosis and coding by physicians, possibly reducing the duration of the SMA clinical diagnostic process. This would improve Malaffi data accuracy and importantly improve early treatment and diagnosis of SMA.*

Limitation 3: The data indicates that a greater number of SMA medications are being prescribed compared to the number that are being dispensed to patients. As a result, it is uncertain whether SMA patients are receiving the necessary treatment.

> ***Recommendation 3:*** *Further investigation is warranted to determine the causes of the discrepancies between the prescribed and distributed medications, and to pinpoint the barriers that impede access to treatment.*

Limitation 4: There exists a possibility that data related to new-born and deceased patients is incomplete since there was no record of patients' birth weights and death flags were only captured for 5 patients. Since the data set included Emirati and expatriate patients the possibility that death data may not be documented in the Malaffi database or in the Abu Dhabi Death registry is acknowledged.

> ***Recommendation 4:*** *Ensuring the accuracy of information relating to new-born and deceased patients may be improved by linking the birth and death records stored in the wider national birth and death registries, particularly within the UAE, with the Malaffi database.*

Limitation 5: The retrospective analysis study design has inherent limitations. It is important to note that these limitations do not diminish the significance or value of the study's findings. Acknowledging these limitations is crucial for advancing future SMA research and avoiding replication of the same study design.

Specific limitations include: (a) selection bias due to the sole use of Malaffi and Abu Dhabi death registry data, and (b) the inability of retrospective designs to consider all potentially confounding variables that may influence study endpoints.

> ***Recommendation 5(a):*** *Future studies should consider using multiple data resources such as surveys, medical records, or administrative databases. This can help to ensure that your study population is more representative of the wider population.*
>
> ***Recommendation 5(b)****: Future studies may consider the use of prospective study designs.*

6. Summary

This study sheds light into the current status of SMA in Abu Dhabi via the analysis of Malaffi data between January 1st 2021 and September 21st 2022. In summary, the prevalence of SMA in Abu Dhabi in 2021 was estimated at 1 in 12,290 individuals, with a total of 150 SMA patients identified in Abu Dhabi via the Malaffi database (SMA1 = 12 pts.; other types of SMA = 138 pts.). Caution has been given regarding comparing the prevalence of SMA in Abu Dhabi with those of specific countries since a systematic review conducted in 2017 identified that the incidence and prevalence of SMA differ between available studies[19]. The authors attributed these differences to diagnostic reliance on clinical findings rather than genetic testing, as well as the small size of the studies. This being said, our data does suggest that the prevalence of SMA in Abu Dhabi is lower that the global reported estimate of 1 in 10,000[1, 2].

SMA patients were predominantly male and Emirati. This may be related to the increased number of consanguineous marriages in the Emirati versus expatriate populations[20]. Further, 95% of SMA cases are caused by homozygous deletions in the SMN1 gene which is located on the X chromosome[4]. In females, if a mutated X chromosome is inherited, the second X chromosome can often produce enough SMN protein to compensate for the loss of function in the mutated chromosome. However, since males have just one X chromosome, if the SMN1 gene is mutated/ deleted, the individual will likely present with SMA. For this reason, SMA is more common in males, as we see also in our data.

The average age at the time of diagnosis for SMA1 patients was 6 months, which is in line with the literature[8, 9]. However, the average age at the time of diagnosis for all other types of SMA (17 years) could not be compared with previously published data since 'other types of SMA' includes SMA2, SMA3, and SMA4 combined. Further, this study could not definitively identify the SMA diagnostic techniques currently used in Abu Dhabi. Data revealed that muscle biopsy was the only recorded diagnostic test which was conducted for just 1 SMA patient. This is interesting since the globally used gold standard diagnostic test for SMA is genetic testing. For example, a Japanese nationwide epidemiological survey identified 658 SMA patients in 2017, with a genetic testing rate of 79.5%**[21].** Further, 246 facilities confirmed the presence of patients with SMA within their Japanese medical facilities, with 43 other facilities involved in the SMA patient pathway. Within these facilities, paediatricians were identified as the clinical specialty most actively involved in managing the condition. Our data revealed an average time to diagnosis of 32 ± 32 days for SMA1 patients and 139 ± 239 days for other SMA types. However, this data is based on only 6 SMA1 patients and 73 patients with 'other types of SMA' which encompasses SMA1 outliers, SMA2, SMA3 and SMA4 patients. Due to the small sample size, and the inability to define the number of patients with SMA2, SMA3, and SMA4, we did not compare 'time to diagnosis' data with global estimates. The most

frequently reported SMA-related symptoms, co-morbidities, and services were related to musculoskeletal, respiratory, and gastro-intestinal systems, as well as feeding and dehydration. All of which are in line with those reported in the International Standards of Care for SMA[22].

Finally, more SMA medications were prescribed for patients than were dispensed, with risdiplam being the most prescribed and only dispensed treatment. This is critical since the age at which treatment is initiated, particularly when it occurs before symptoms manifest (pre-symptomatic treatment initiation), is the most crucial determinant of treatment success and disease prognosis[23]. Early detection of SMA may be facilitated via new-born screening (NBS) programs which are now becoming more prevalent worldwide[24]. In 2021, a global survey including 152 countries identified 9 SMA NBS programs across Taiwan, USA, Germany, Belgium, Australia, Italy, Russia, Canada, and Japan. The respondents of these 9 countries reported 288 new-borns diagnosed with SMA out of 3,674,277 new-borns screened. This corresponds to an incidence rate of 1 in 12,757[24]. Unfortunately, several endpoints in our study related to treatment could not be determined due to incomplete/ missing data, to include diagnosis-to-treatment ratio, and time-to-treatment. Future studies may seek to elucidate these endpoints to provide a more comprehensive understanding of the clinical burden of SMA.

Overall, the clinical burden of SMA in Abu Dhabi is substantial, as reported worldwide, and can be attributed to multiple factors. SMA is a progressive disease that requires continuous support and monitoring from healthcare professionals, including medicinal treatment, physical therapies, and other SMA-related supportive and life-prolonging services. The onset of the most severe form of SMA (SMA1) occurs within the first 6 months of a child's life, which means that affected individuals will experience the burden of SMA for most of their life. This can negatively impact their development, education, and overall quality of life. Finally, SMA is a heterogeneous disease meaning it is caused by a range of genetic variations and subtypes that can present with different severities, age of onset and a wide spectrum of symptoms. This often makes the disease difficult to diagnose leading to diagnostic and treatment delays which may be life threatening.

7. Appendices

Appendix 1: Demographic Table

Characteristics	SMA1	Other SMA Types					
	G12.0	G12.0 outliers	G12.1	G12.8	G12.9	**Other SMA Types: Total**	**Total**
Total no. of patients, n (%)	**12 (8)**	25 (17)	30 (20)	10 (7)	73 (49)	**138 (92)**	**150 (100)**
Age at index date							
Yrs; mean ± SD	0.5±0.3	11.2±18.4	18.8±21.1	21.1±24	18.5±19.5	17.4±20.2	16.1±19.9
Yrs; min-max	0.05-0.9	1.54-70.5	0.39-71.3	0.29-72.4	0.16-97.4	0.16 – 97.4	0.05-97.4
Infants: >0, ≤ 1 year, n (%)	12 (100)	-	3 (10)	3 (30)	13 (18)	19 (14)	31 (21)
Children: >1, ≤12 years, n (%)	-	18 (72)	14 947)	2 (20)	26 (36)	60 (43)	60 (40)
Youths: >12, ≤18 years, n (%)	-	4 (16)	4 (13)	-	4 (5)	12 (9)	12 (8)
Adults: >18, ≤30 years, n (%)	-	-	3 (10)	2 (20)	10 (14)	15 (11)	15 (10)
Adults: >30, ≤40 years, n (%)	-	1 (4)	2 (7)	1 (10)	8 (11)	12 (9)	12 (8)
Adults: >40, ≤ 50 years, n (%)	-	1 (4)	-	1 (10)	7 (10)	9 (7)	9 (6)
Adults: >50, <65 years, n (%)	-	-	-	-	2 (3)	2 (1)	2 (1)
Elderly: ≥ 65 years, n (%)	-	1 (4)	4 (13)	1(10)	3 (4)	9 (7)	9 (6)
Age at final diagnosis							
Yrs; mean ± SD	2.8±2.9	13.8±15.4	21±20.7	22.9±23.7	20.4±19.9	19.5±19.6	18.2±19.4
Yrs; min-max	0.09-9.9	1.55-70.5	0.73-71.5	0.67-72.7	0.21-97.8	0.21 – 97.8	0.09-97.8
Age at data analysis (25 April 2023)							
Yrs; mean ± SD	3.9±3	14.9±15.5	22±20.8	24.2±23.7	21.7±20	20.7±19.7	19.3±19.5
Yrs; min-max	0.82-11.7	2.9-72.4	2.07-72.4	2.23-73.6	1.65-98.4	1.65-98.4	0.82-98.4
Sex, n (%)							
Female	4 (33)	12 (48)	11 (37)	4 (40)	33 (45)	60 (43)	64 (43)
Male	8 (67)	13 (52)	19 (63)	6 (60)	40 (55)	78 (57)	86 (57)
Nationality, n (%)							
Emirati	6 (50)	19 (76)	20 (67)	8 (80)	40 (55)	87 (63)	93 (62)
Expatriate	6 (50)	6 (24)	10 (33)	2 (20)	33 (45)	51 (37)	57 (38)
Death Flag							
Yes (n%)	3 (25)	-	1 (3)	-	1 (1)	2 (1)	5 (3)
Age at death flag Yrs; mean ± SD	5.1±4.8	-	71.9	-	10	41±43.7	19.4±29.6

*G12.0 outliers represent secondary analysis data only.
- means no patients
Abbreviations: Yrs = years, n = number of patients, SD = standard deviation,

Appendix 2: Annual Diagnosis Counts

	G12.0	G12.0 outliers[1]	G12.1	G12.8	G12.9	Total	Cumulative Total
Patients diagnosed before 2021	6	16	15	4	30	71	71
New patients diagnosed in 2021[2]	5	7	9	3	28	52	123
New patients diagnosed in 2022[3]	1	2	6	3	15	27	150

[1] G12.0 outliers represent secondary analysis data only.
[2] SMA prevalence in 2021 = cumulative total (123)/ total population (1,511,768) = 0.008% or 1 in 12,290 individuals.
[3] 2022 data represents an incomplete year. Cumulative total includes data between January 1st to September 21st 2022.
Abbreviations: n = number of patients.

Appendix 3: SMA-Related Symptoms

Characteristics	SMA Type 1	Other SMA Types					Total
ICD-10 Code	G12.0	G12.0 outliers	G12.1	G12.8	G12.9	Subtotal	
Total no. of encounters, n(%)	**450 (12)**	**489 (13)**	**670 (18)**	**106 (3)**	**1962 (53)**	**3227 (88)**	**3677 (100)**
SMA-related symptoms							
Muskoloskeletal	116 (6)	210 (12)	438 (24)	54 (3)	982 (55)	1684 (94)	**1800 (100)**
M41.9 Scoliosis, unspecified	63 (54)	77 (37)	132 (30)	2 (4)	324 (33)	535 (32)	**598 (33)**
M62.81 Muscle weakness (generalized)	15 (13)	31 (15)	143 (33)	22 (41)	367 (37)	563 (33)	**578 (32)**
R25.2 Cramp and spasm	(0)	42 (20)	72 (16)	15 (28)	50 (5)	179 (11)	**179 (10)**
M41.55 Other secondary scoliosis, thoracolumbar region	(0)	(0)	7 (2)	(0)	94 (10)	101 (6)	**101 (6)**
M41.85 Other forms of scoliosis, thoracolumbar region	(0)	15 (7)	29 (7)	2 (4)	32 (3)	78 (5)	**78 (4)**
M41.45 Neuromuscular scoliosis, thoracolumbar region	1 (1)	10 (5)	15 (3)	(0)	21 (2)	46 (3)	**47 (3)**
M41.40 Neuromuscular scoliosis, site unspecified	4 (3)	17 (8)	16 (4)	(0)	9 (1)	42 (2)	**46 (3)**
M41.44 Neuromuscular scoliosis, thoracic region	18 (16)	(0)	1 (0)	12 (22)	10 (1)	23 (1)	**41 (2)**
M41.80 Other forms of scoliosis, site unspecified	3 (3)	4 (2)	7 (2)	(0)	14 (1)	25 (1)	**28 (2)**
R27.8 Other lack of coordination	7 (6)	4 (2)	5 (1)	(0)	9 (1)	18 (1)	**25 (1)**
M41.84 Other forms of scoliosis, thoracic region	3 (3)	1 (0)	1 (0)	(0)	16 (2)	18 (1)	**21 (1)**
M41.46 Neuromuscular scoliosis, lumbar region	(0)	2 (1)	(0)	(0)	16 (2)	18 (1)	**18 (1)**
M41.86 Other forms of scoliosis, lumbar region	(0)	2 (1)	2 (0)	(0)	8 (1)	12 (1)	**12 (1)**
Z47.82 Encounter for orthopedic aftercare following scoliosis surgery	(0)	4 (2)	5 (1)	(0)	1 (0)	10 (1)	**10 (1)**
R25.1 Tremor, unspecified	2 (2)	(0)	(0)	(0)	2 (0)	2 (0)	**4 (0)**
M41.47 Neuromuscular scoliosis, lumbosacral region	(0)	(0)	1 (0)	(0)	2 (0)	3 (0)	**3 (0)**
M41.54 Other secondary scoliosis, thoracic region	(0)	(0)	(0)	(0)	3 (0)	3 (0)	**3 (0)**
G25.9 Extrapyramidal and movement disorder, unspecified	(0)	(0)	2 (0)	(0)	(0)	2 (0)	**2 (0)**
M41.34 Thoracogenic scoliosis, thoracic region	(0)	(0)	(0)	(0)	2 (0)	2 (0)	**2 (0)**
M41.35 Thoracogenic scoliosis, thoracolumbar region	(0)	1 (0)	(0)	(0)	1 (0)	2 (0)	**2 (0)**
R26.0 Ataxic gait	(0)	(0)	(0)	(0)	1 (0)	1 (0)	**1 (0)**
R26.1 Paralytic gait	(0)	(0)	(0)	1 (2)	(0)	1 (0)	**1 (0)**
Respiratory	50 (16)	63 (20)	27 (9)	23 (7)	145 (47)	258 (84)	**308 (100)**
J96.90 Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia	10 (20)	40 (63)	7 (26)	1 (4)	56 (39)	104 (40)	**114 (37)**
J96.00 Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	16 (32)	7 (11)	13 (48)	14 (61)	17 (12)	51 (20)	**67 (22)**
J96.01 Acute respiratory failure with hypoxia	8 (16)	(0)	2 (7)	8 (35)	16 (11)	26 (10)	**34 (11)**
J47.9 Bronchiectasis, uncomplicated	3 (6)	(0)	(0)	(0)	27 (19)	27 (10)	**30 (10)**
J44.9 Chronic obstructive pulmonary disease, unspecified	(0)	(0)	(0)	(0)	19 (13)	19 (7)	**19 (6)**
J96.02 Acute respiratory failure with hypercapnia	9 (18)	2 (3)	4 (15)	(0)	3 (2)	9 (3)	**18 (6)**
J98.09 Other diseases of bronchus, not elsewhere classified	1 (2)	8 (13)	(0)	(0)	1 (1)	9 (3)	**10 (3)**
J96.92 Respiratory failure, unspecified with hypercapnia	(0)	5 (8)	(0)	(0)	2 (1)	7 (3)	**7 (2)**
J96.91 Respiratory failure, unspecified with hypoxia	(0)	1 (2)	1 (4)	(0)	3 (2)	5 (2)	**5 (2)**
P28.5 Respiratory failure of newborn	2 (4)	(0)	(0)	(0)	(0)	0 (0)	**2 (1)**
P22.9 Respiratory distress of newborn, unspecified	1 (2)	(0)	(0)	(0)	(0)	0 (0)	**1 (0)**
P28.4 Other apnea of newborn	(0)	(0)	(0)	(0)	1 (1)	1 (0)	**1 (0)**
Nutrition & feeding	154 (14)	144 (13)	179 (17)	22 (2)	585 (54)	930 (86)	**1084 (100)**
R63.3 Feeding difficulties	64 (42)	75 (52)	62 (35)	14 (64)	250 (43)	401 (43)	**465 (43)**
R13.10 Dysphagia, unspecified	34 (22)	43 (30)	68 (38)	2 (9)	190 (32)	303 (33)	**337 (31)**
E86.0 Dehydration	32 (21)	24 (17)	30 (17)	5 (23)	104 (18)	163 (18)	**195 (18)**
R13.12 Dysphagia, oropharyngeal phase	11 (7)	1 (1)	13 (7)	1 (5)	15 (3)	30 (3)	**41 (4)**
P92.9 Feeding problem of newborn, unspecified	1 (1)	1 (1)	2 (1)	(0)	13 (2)	16 (2)	**17 (2)**
R13.11 Dysphagia, oral phase	(0)	(0)	2 (1)	(0)	11 (2)	13 (1)	**13 (1)**
R13.13 Dysphagia, pharyngeal phase	5 (3)	(0)	1 (1)	(0)	2 (0)	3 (0)	**8 (1)**
P92.3 Underfeeding of newborn	3 (2)	(0)	(0)	(0)	(0)	0 (0)	**3 (0)**
F98.29 Other feeding disorders of infancy and early childhood	1 (1)	(0)	(0)	(0)	(0)	0 (0)	**1 (0)**
P74.1 Dehydration of newborn	1 (1)	(0)	(0)	(0)	(0)	0 (0)	**1 (0)**
P78.83 Newborn esophageal reflux	1 (1)	(0)	(0)	(0)	(0)	0 (0)	**1 (0)**
P92.5 Neonatal difficulty in feeding at breast	1 (1)	(0)	(0)	(0)	(0)	0 (0)	**1 (0)**
R13.0 Aphagia	(0)	(0)	1 (1)	(0)	(0)	1 (0)	**1 (0)**
Developmental Milestones	164 (13)	298 (23)	212 (17)	22 (2)	578 (45)	1110 (87)	**1274 (100)**
R62.51 Failure to thrive (child)	130 (79)	72 (24)	26 (12)	6 (27)	250 (43)	354 (32)	**484 (38)**
R62.0 Delayed milestone in childhood	13 (8)	180 (60)	121 (57)	10 (45)	112 (19)	423 (38)	**436 (34)**
R62.50 Unspecified lack of expected normal physiological development in childhood	18 (11)	45 (15)	63 (30)	5 (23)	209 (36)	322 (29)	**340 (27)**
R62.59 Other lack of expected normal physiological development in childhood	(0)	1 (0)	1 (0)	(0)	7 (1)	9 (1)	**9 (1)**
R62.52 Short stature (child)	3 (2)	(0)	1 (0)	(0)	(0)	1 (0)	**4 (0)**
R62.7 Adult failure to thrive	(0)	(0)	(0)	1 (5)	(0)	1 (0)	**1 (0)**

Appendix 4: SMA-Related Co-morbidities

Characteristics	SMA Type 1	Other SMA Types				Total
ICD-10 Code	G12.0	G12.0 outliers	G12.1	G12.8	G12.9	Subtotal
Total no. of encounters, n(%)	**141 (13)**	**102 (10)**	**327 (31)**	**23 (2)**	**468 (44)**	**920 (87)**	**1061 (100)**
SMA-related Comorbidities							
Cardiovascular	2 (1)	49 (25)	64 (32)	1 (1)	82 (41)	196 (99)	**198 (100)**
I10 Essential (primary) hypertension	2 (100)	49 (100)	64 (100)	1 (100)	79 (96)	193 (98)	**195 (98)**
I50.9 Heart failure, unspecified	(0)	(0)	(0)	(0)	3 (4)	3 (2)	**3 (2)**
Gastrointestinal	110 (16)	43 (6)	246 (36)	20 (3)	260 (38)	569 (84)	**679 (100)**
K21.9 Gastro-esophageal reflux disease without esophagitis	98 (89)	41 (95)	241 (98)	16 (80)	243 (93)	541 (95)	**639 (94)**
K21.0 Gastro-esophageal reflux disease with esophagitis	12 (11)	2 (5)	5 (2)	1 (5)	14 (5)	22 (4)	**34 (5)**
R12 Heartburn	(0)	(0)	(0)	3 (15)	2 (1)	5 (1)	**5 (1)**
K59.9 Functional intestinal disorder, unspecified	(0)	(0)	(0)	(0)	1 (0)	1 (0)	**1 (0)**
Nutrition & feeding	(0)	1 (2)	(0)	(0)	53 (98)	54 (100)	**54 (100)**
Z79.4 Long term (current) use of insulin	(0)	(0)	(0)	(0)	52 (98)	52 (96)	**52 (96)**
E46 Unspecified protein-calorie malnutrition	(0)	1 (100)	(0)	(0)	1 (2)	2 (4)	**2 (4)**
Respiratory	29 (22)	9 (7)	17 (13)	2 (2)	73 (56)	101 (78)	**130 (100)**
J18.9 Pneumonia, unspecified organism	29 (100)	9 (100)	17 (100)	2 (100)	73 (100)	101 (100)	**130 (100)**

Appendix 5: SMA-Related Services

Characteristics	SMA Type 1	Other SMA Types				Total
Codes	G12.0	G12.0 outliers	G12.1	G12.8	G12.9	Subtotal
Total no. of patients, n(%)	**12 (8)**	**25 (17)**	**30 (20)**	**10 (7)**	**73 (49)**	**138 (92)**	**150 (100)**
SMA-related services							
Patients with available CPT4 codes	**6 (4)**	**8 (5)**	**4 (3)**	**3 (2)**	**16 (11)**	**31 (21)**	**37 (25)**
CPT4 codes							
31500 Intubation, endotracheal, emergency procedure	**4 (67)**	4 (50)	3 (75)	2 (67)	10 (63)	**19 (61)**	**23 (62)**
43760 Change of gastrostomy tube, percutaneous, without imaging or endoscopic guidance	**2 (33)**	5 (63)	1 (25)	1 (33)	9 (56)	**16 (52)**	**18 (49)**
43280 Laparoscopy, surgical, esophagogastric fundoplasty (eg, Nissen, Toupet procedures)	**1 (17)**	1 (13)	(0)	(0)	2 (13)	**3 (10)**	**4 (11)**
22899 Unlisted procedure spine - Percutaneous posterior spinal fixation from Thoracic Spine D12 to Lumbar Spine L4	**(0)**	1 (13)	1 (25)	(0)	(0)	**2 (6)**	**2 (5)**
22842 Posterior segmental instrumentation (eg, pedicle fixation, dual rods with multiple hooks and sublaminar wires); 3 to 6 vertebral segments (List separately in addition to code for primary procedure)	**(0)**	(0)	1 (25)	(0)	(0)	**1 (3)**	**1 (3)**
22844 Posterior segmental instrumentation (eg, pedicle fixation, dual rods with multiple hooks and sublaminar wires); 13 or more vertebral segments (List separately in addition to code for primary procedure)	**(0)**	(0)	(0)	(0)	1 (6)	**1 (3)**	**1 (3)**
94002 Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day	**(0)**	(0)	(0)	(0)	1 (6)	**1 (3)**	**1 (3)**
94003 Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day	**(0)**	(0)	(0)	(0)	1 (6)	**1 (3)**	**1 (3)**
94010 Spirometry, including graphic record, total and timed vital capacity, expiratory flow rate measurement(s), with or without maximal voluntary ventilation	**(0)**	(0)	(0)	1 (33)	(0)	**1 (3)**	**1 (3)**
94660 Continuous positive airway pressure ventilation (CPAP), initiation and management	**(0)**	(0)	(0)	(0)	1 (6)	**1 (3)**	**1 (3)**
97110 Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility	**(0)**	(0)	1 (25)	(0)	(0)	**1 (3)**	**1 (3)**
97112 Therapeutic procedure, 1 or more areas, each 15 minutes; neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities	**(0)**	(0)	1 (25)	(0)	(0)	**1 (3)**	**1 (3)**
99503 Home visit for respiratory therapy care (eg, bronchodilator, oxygen therapy, respiratory assessment, apnea evaluation)	**(0)**	(0)	1 (25)	(0)	(0)	**1 (3)**	**1 (3)**
Patients with available ICD-10 codes	**10 (7)**	**18 (12)**	**9 (6)**	**4 (3)**	**38 (25)**	**69 (46)**	**79 (53)**
ICD-10 Code							
Z71.3 Dietary counseling and surveillance	6 (60)	12 (67)	6 (67)	3 (75)	27 (71)	48 (70)	**54 (68)**
Z93.0 Tracheostomy status	6 (60)	15 (83)	3 (33)	2 (50)	20 (53)	40 (58)	**46 (58)**
Z99.11 Dependence on respirator [ventilator] status	8 (80)	14 (78)	6 (67)	2 (50)	15 (39)	37 (54)	**45 (57)**
J96.10 Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	9 (90)	14 (78)	2 (22)	2 (50)	17 (45)	35 (51)	**44 (56)**
Z99.89 Dependence on other enabling machines and devices	3 (30)	4 (22)	4 (44)	1 (25)	11 (29)	20 (29)	**23 (29)**
J95.01 Hemorrhage from tracheostomy stoma	2 (20)	4 (22)	0 (0)	0 (0)	8 (21)	12 (17)	**14 (18)**
J95.850 Mechanical complication of respirator	0 (0)	1 (6)	0 (0)	0 (0)	3 (8)	4 (6)	**4 (5)**

Appendix 6: Glossary

Time to diagnosis	The time taken from the first recorded SMA symptom to index date.
Diagnosis-to-treatment ratio	The ratio between the number of individuals diagnosed with SMA and the number of individuals who received SMA treatment, which indicates the extent to which people are being diagnosed without receiving treatment. A high diagnosis-to-treatment ratio implies that a larger number of people are diagnosed with SMA compared to the number of people who actually receive treatment.
Encounter	An instance of a patient visiting a healthcare provider, as a result of which a record is been made in the patient's EHR.
Final diagnosis	The final diagnosis is the date of last diagnosis of SMA by record of an SMA related ICD-10 code in the patients EHR (i.e., G12.0, G12.1, G12.8, or G12.9) within the project period (January 1st, 2021, to September 21st, 2022).
Index date	The index date is the date of first diagnosis of SMA by record of an SMA related ICD-10 code in the patients EHR (i.e., G12.0, G12.1, G12.8, or G12.9).
Medical history	Medical history refers to the record of a person's past medical conditions, treatments, and diagnoses, including information about surgeries, and medications in the Malaffi database.
Mortality rate	The mortality rate is a measure of the number of deaths in a population over the study period, expressed as a ratio of the number of deaths to the size of the population or as a rate per unit of population.
Other SMA types	Includes patients diagnosed with G12.1, G12.8 and G12.9, as well as G12.0 outliers. These codes encompas SMA2, SM3, and SM4.
Project duration	The project duration ranged from January 1st, 2021, to September 21st, 2022. However, the analysis of SMA symptoms and diagnosis data was analysed across the entire medical history preceding the index date as this data is part of the clinical diagnostic workup.
Time-to-treatment	The time between the index date and the date treatment is dispensed.
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]
G12.0 outliers	Patients first diagnosed with SMA1 (G12.0) aged >1 year
G12.1	Other inherited spinal muscular atrophy
G12.8	Other spinal muscular atrophies and related syndromes
G12.9	Spinal muscular atrophy, unspecified

Appendix 7: Abbreviations

CPT4	Current Procedural Terminology, 4th Edition
DOH	Department of Health
EHR	Electronic health record
EMA	European Medicines Agency
GERDs	Gastro-oesophageal reflux disease
ICD-10	International Classification of Diseases, Tenth Revision
IROS	Insights Research Organization & Solutions
FDA	Food and Drug Administration
MOHAP	Ministry of Health and Prevention
NBS	New-born screening
pt(s)	Patients
RWD	Real-world data
RWE	Real-world evidence
SMA	Spinal muscular atrophy
SMA1	Spinal muscular atrophy type 1
SMA2	Spinal muscular atrophy type 2
SMA3	Spinal muscular atrophy type 3
SMA4	Spinal muscular atrophy type 4
SMN1	Survival motor neuron-1
UAE	United Arab Emirates

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