WITHDRAWN: Indications, Contraindications, and Some Side Effects of Hyperbaric Oxygen Therapy (HBOT) in Children With Special Needs: *A Cross-sectional Study*

Dr. Khalid M Zayed

Drzayed@outlook.com

Ain Shams University

Research Article

Keywords: Hyperbaric Oxygen Therapy, HBOT, Pediatrics, Special needs, Middle Ear Barotrauma, Tympanometry, modified Teed Score, Hamilton Anxiety Score

Posted Date: June 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1771811/v1

EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background: Hyperbaric oxygen therapy (HBOT) is a treatment modality in which a subject breathes 100% O_2 under increased atmospheric pressure, typically 2-3 Atmospheres Absolute (ATA) in mono- or multiplace chambers. HBOT is provided in a variety of clinical settings by providers with varying levels of expertise. It is an important advanced therapy in the treatment of at least fourteen documented ailments.

Objective: To study indications, contraindications, and some side effects of hyperbaric oxygen in a group of children with special needs.

Methodology: Data for this study were collected from a sample of purposefully selected 100 (69 male+31 female) patients with special needs from a center in Cairo (age range: 72-120 months) to address the aim of the study by the use of different tools: 1. Cases' parents' interview form. 2. Full medical history, examination, and investigations. 3. Employing some clinical tests such as tympanometry as well as modified Teed and HAM-A Scores to quantify MEB and anxiety side effects of HBOT. 4. Analysis of data. 5. Suggestions for future improvement of HBOT side effects identification and management.

Results: 59% of patients were underweight, 61% stunted, and 58% microcephalic who generally lived in high crowding index environments. They are treated with HBOT and other therapies for LD (38%), CP (36%), ASD (20%), ADHD (4%), and Wounds (2%) and had 2203 sessions in 24 months. For middle ear condition, tympanometry showed that 78 patients had Type A (5 Type AD & 6 Type AS), 6 Type B & 4 Type C. M-Teed score showed that 56% had grade 0, 24% grade 1, 10% grade 2, 3% grade 3, 1% grade 4, and 6% grade 5. For claustrophobia, the Anxiety Severity HAM-A score showed that only 2% had moderate to severe symptoms. 47% of parents were satisfied with the treatments, 35% neutral, and 18% dissatisfied.

Conclusion: HBOT remains among the safest therapies used today, especially in the pediatric population with special needs even though there are a few contraindications and side effects associated with it. It is both its primary and secondary effects that result in its benefits as well as side effects. Even though they were found to be infrequent and mild, providers need to be able to identify, understand, and quantify these potential side effects such as MEB and claustrophobia for prevention, management, and informed consent. One of the most common side effects identified in the peer-reviewed literature is MEB. It is typically mild and self-limited. Patient instruction on middle ear clearing, daily monitoring with an otoscopic examination, and appropriate compression rates are important to its prevention. Claustrophobia or confinement anxiety in monoplace chambers is another side effect of HBOT but it is generally mild and anxiety is easily controlled with sedation before treatments so that individuals may continue to receive daily HBOT. Preventive measures with adequate patient history, patient education, reassurance, and coaching are the most effective means of anticipating episodes of claustrophobia and treating them effectively before HBOT.

1) Introduction

Hyperbaric oxygen (HBO_2) therapy is a treatment modality in which a subject breathes 100% O_2 under increased atmospheric pressure, typically 2-3 Atmospheres Absolute (ATA) (i.e. the sum of the atmospheric pressure (1 ATA) plus extra hydrostatic pressure equal to one or two atmospheres[2]). Treatments are done in either a mono- (single person) or multi-place (usually 2 to 14 patients) chamber ***[1]***, ***[2]***. Its primary and secondary effects can cause beneficial, as well as side effects. Although HBOT was not studied in medical school curricula and had no pharmaceutical companies to support it, HBO_2 is now commonly and promptly gaining acceptance due to numerous reasons including:

a. It is a safe remedy with rare and minor documented side effects.
b. Its addition obviates the need for several surgical procedures and promotes healing and early mobility of patients.
c. It reduces hospitalization length, treatment, and costs of rehabilitation.
d. In some situations, it is the only treatment available.
e. It has an emergent role in indications for permanent disabilities ***[3]***.

According to indication, HBO_2 treatments may last 1.5 to 8 hours and may be performed 1-3 times a day. The monoplace chambers are customarily compressed with pure O_2, while multiplace chambers are pressurized with air where subjects can breathe pure O_2 through a tight-fitting face mask, a head tent, or an endotracheal tube. During treatment, the arterial O_2 tension frequently exceeds 2000 mmHg and tissue levels of 200-400 mmHg can result ***[2]***. At normal atmospheric pressure, O_2 transport is limited by the O_2 binding capacity to the RBCs' hemoglobin while a little O_2 is transported by blood plasma. O_2 transport by plasma is significantly increased using HBOT because of O_2's higher solubility with increasing pressure following Henry's law[3] rather than the RBCs' hemoglobin where the route of transport cannot be utilized any further being almost saturated with O_2 at 1 atmospheric pressure ***[4]***.

The healing principle of HBOT lies in its capacity to significantly increase the partial pressure of O_2 in the body tissues where the partial pressures attainable using HBOT are much greater than those achievable while breathing pure O_2 under normobaric conditions via an increase in the O_2 transport capacity of the blood. HBOT curative effects are dependent on both hydrostatic pressure and the partial pressure of O_2 as an elevation of the hydrostatic pressure causes a reduction in the gas volume according to Boyle's law[4]. This action directly relates to pathologic conditions in which gas bubbles are present in the body like arterial gas embolism and decompression sickness [5]. Most of the patients who undergo HBOT are not treated for bubble-induced injuries because the healing mechanisms are related to an elevated PaO_2 ***[6]***, ***[7]***. The results of HBOT include both primary and secondary effects. The primary effects cause increased pressure and hyperoxia while the secondary effects (resulting from controlled oxidative stress) include antimicrobial ischemia-reperfusion injuries blunting, and wound healing—a result of both local and systemic effects. Again, the local effects include a steepened O_2 gradient, macrophage pooling, and

multiple growth factors release while the systemic effects result in progenitor stem cell mobilization and release from bone marrow in addition to enhanced homing to the injury's site by these cells **[2]** ***[8]***, by a nitrous oxide (·NO)-dependent mechanism. These effects can result in neovasculogenesis and collagen formation that promote wound healing ***[8]***.

1.1 General HBOT Indications

Hypoxia is a substantial component of the pathology of stroke, cancer, heart disease, and chronic lung disease—accounting for almost 60% of the total number of deaths—because hypoxia leads to metabolic acidosis, organ dysfunction, and death ***[10]***. The conventional O_2 therapy may not bring about the wanted results but HBOT yields remarkable clinical developments. O_2 is necessary for adequate carbohydrates metabolism and adenosine triphosphates (ATP) production. When O_2 levels do not meet the requirements of body function, tissue hypoxia occurs. Generally, O_2 therapy is indicated in hypoxemia to eliminate tissue hypoxia, which may cause a series of adverse problems, such as localized vasodilation, pulmonary vasoconstriction, metabolic acidosis, tissue necrosis, an increased risk of kernicterus, brain injury, and impairment of surfactant production, especially in the pediatric population ***[11]***.

Recommendations for HBO_2 use are given by The Undersea and Hyperbaric Medical Society (UHMS), which is a devoted team of doctors and researchers who study the use of HBO, and approved use of HBO_2 for the treatment of fourteen conditions, including decompression illness, air or gas embolism, CO poisoning, arterial insufficiencies, enhancement of healing in selected non-healing problem wounds, compromised non-healing refractory grafts and flaps, certain bone or skin infections, non-healing or decubitus (bed sores) ulcers, necrotizing soft tissue infections, intracranial abscess, refractory osteomyelitis, crush injury, clostridial myositis, and myonecrosis, compartment syndrome, and other acute traumatic ischaemias, severe anemia, delayed radiation soft tissue injury and acute thermal burn injury as well as those with acute sensorineural hearing loss and many neurological illnesses that can benefit from HBOT. The UHMS Hyperbaric Oxygen Therapy Committee lists approvals for reimbursement for certain diagnoses in hospitals and clinics (Table 1) ***[12], [13], [14], [15].***

Table 1: FDA-approved and UHMS-reimbursable indications for hyperbaric oxygen therapy.

No	Indication
1	Air or gas embolism
2	Carbon monoxide poisoning; cyanide poisoning; smoke inhalation
3	Clostridial myositis and myonecrosis (gas gangrene)
4	Crush injuries, compartment syndromes, and other acute traumatic peripheral ischemias
5	Decompression sickness
6	Enhancement of healing in selected problem wounds
7	Exceptional blood loss anemia
8	Intracranial abscess
9	Necrotizing soft tissue infections
10	Refractory osteomyelitis
11	Skin flaps and grafts (compromised)
12	Delayed radiation injury (soft tissue and bony necrosis)
13	Thermal burns

Research demonstrates that HBOT prevents 75% of all major amputations that may result from diabetic wounds and a 450% increase in complete recovery in subjects with traumatic brain injury getting HBOT *vs.* standard intensive care. In addition, new applications of HBOT are in effect in emergency care settings for resuscitation in acute hemorrhage, near drowning, hanging, poisoning, and cardiorespiratory arrest *[16]* **.** The FDA approved HBOT for the treatment of many conditions such as autism, stroke, air embolism, ischemic limbs, split-thickness skin graft acceptance, failed grafts, flap survival/salvage, wound reepithelialization, acute thermal burns, etc. *[3]* .

The addition of HBOT in cases of acute traumatic wounds, crush injuries, compartment syndrome, gas gangrene, and burns may be life and/or limb saving and the use of hyperbaric medicine in foot or brain wounds, strokes, and neurological diseases with poor prognoses treatment is a gift where great advances are being made ***[15]*** , ***[17].*** Moreover, with the application of isotopic tracers, magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT), HBOT is getting evidence-based recognition in the modern era with continuing global growth with many public and private hyperbaric facilities ***[16]*** . HBOT indications are diverse, some of which are shown below (Table 2).

Table 2: Indications for Hyperbaric Oxygen Therapy.

A. UNIVERSALLY ACCEPTED: These indications are supported with peer-reviewed proof of efficacy.	
Primary Line of Treatment	• Air or gas embolism [18]. • Decompression sickness [19], [20], [21]. • Carbon monoxide poisoning, smoke inhalation ***[22]***, [23]. • Carbon monoxide poisoning complicated by cyanide poisoning [24], [25], [26].
Wounds	• Enhancement of healing in selected problem wounds, and ulcers (diabetic, venous, etc) [27], [28]. • Diabetically derived illness, such as short-term relief of diabetic foot [29], [30], [31], diabetic retinopathy [32], diabetic nephropathy [33]. • Mucormycosis, especially rhinocerebral disease in the setting of diabetes mellitus ***[34].*** • Infective wounds: Clostridial myositis and myonecrosis (gas gangrene) [35], [36], [37], refractory osteomyelitis [38], [39], necrotizing soft tissue infections (necrotizing fasciitis) [40], [41]. • Crush injury, compartment syndrome, and other acute traumatic ischemias [42], [43]. • Skin grafts and flaps (compromised) [44]. • Thermal burns [45] • Exceptional blood loss (anemia) [46], [47]. • Central retinal artery occlusion [48].
Oncology	• Delayed radiation-induced tissue damage and complications due to endarteritis (soft tissue and bony necrosis) [49]. • Prophylactically adjunctive to therapeutic radiation and for preparation of surgery or implant procedures in previously irradiated fields [50].
Other Indications	• Idiopathic acute sensorineural hearing loss (SNHL) [51]. • Intracranial abscess [52], [53]. • Bell's palsy.
B. RESEARCH INDICATIONS: The role of HBOT in these indications is being studied in international trials.	
• HBOT in neurological illnesses: cerebral palsy, stroke, head injury ***[15]***, ***[17]***.	
• HBOT as a radiosensitizer in *glioblastoma mutiforme* and re-irradiation of squamous cell carcinoma.	

1.2 HBOT Indications in Children

For the pediatric population, the most common HBOT indications—besides decompression sickness—are acute ischemia, acute severe infection, air embolism, CO poisoning, chronic wounds, and osteomyelitis ***[54]***. Due to the immunomodulatory properties of HBO_2, efforts are also made to use HBOT in atopic dermatitis or inflammatory bowel disease treatment ***[55]***. Optimum HBOT results can be achieved only with close cooperation between pediatricians and hyperbaric medicine teams ***[55]***. In treating a child with

one of the disorders that can benefit from HBOT, all pediatric medicine branches should be involved including the general pediatrician, the neonatal (NICU), and the pediatric (PICU) intensive care units' consultants as well as the pediatric and orthopedic surgeons ***[56]***.

1.3 Contraindications of hyperbaric oxygen

The only absolute contraindication to HBOT is untreated pneumothorax ***[57]***. The reason is the concern of progression to tension pneumothorax, especially during the therapy decompression phase, although treatment on O_2-based tables can prevent this progression ***[58]***. A COPD patient with a large bleb represents a relative contraindication for similar reasons ***[59]***. Also, the treatment may raise the issue of occupational health and safety (OHS) hazards encountered by the therapists ***[60]***. Special considerations must be made by specialist physicians before HBO_2 treatments begin in the case of relative contraindications including ***[57]***:

1. Cardiac disease.
2. COPD with air trapping: Can lead to pneumothorax during treatment.
3. Emphysema with CO_2 retention: This condition can lead to pneumothorax during HBOT due to the rupture of an emphysematous bulla. It can be evaluated by x-ray.
4. High fevers: In most cases, the fever should be lowered before HBOT begins as fevers may predispose to convulsions.
5. History of thoracic surgery: Usually not considered a contraindication. However, there is concern that air may be trapped in scarred lesions, which need to be evaluated prior to considering HBOT.
6. Malignancies: Cancers thrive in blood-rich environments but may be suppressed by high O_2 levels. HBOT of individuals who have cancer presents a problem as HBO_2 both increases blood flow via angiogenesis and also raises O_2 levels. An anti-angiogenic supplement may provide a solution ***[61]***. Research demonstrated that HBO_2 is beneficial in producing stem/progenitor cells and the malignant process is not accelerated ***[8], [62]***.
7. Middle ear barotrauma (MEB): This is always a consideration in treating both children and adults in a hyperbaric environment because of the necessity to equalize ear pressure ***[63]***.
8. Upper respiratory infections: These may cause difficulty for the patients to equalize their ears or sinuses leading to ear or sinus squeeze.
9. In pediatrics, there are very few contraindications to HBOT. However, in ductal-dependent lesions in congenital heart diseases, being a potent pulmonary vasodilator, HBOT may cause over-circulation within the pulmonary system. Also, in premature neonates, lower SpO_2 may be sought to decrease the toxic effects of O_2 therapy in retinopathy of prematurity (ROP) or bronchopulmonary dysplasia ***[64].***

1.4 Disadvantages of hyperbaric oxygen

1.4.1 Costs

U.S. physicians (Medical Doctor=MD or Doctor of Osteopathy=DO) may lawfully prescribe HBOT for "off-label" conditions, covered by insurance, such as stroke ***[65]*** , ***[66],*** and migraine [67], ***[68]*** . Such patients are treated in outpatient clinics where a 1-hour HBOT session may cost between $300 and higher in private clinics and over $2,000 in hospitals. In the UK, most HBO_2 units are financed by the National Health Service (NHS), although some, such as those run by Multiple Sclerosis Therapy Centers, are non-profit. In Australia, HBOT is not covered by Medicare as a treatment for multiple sclerosis ***[69]*** . China and Russia treat more than 80 conditions with HBOT ***[70]*** . In Egypt, on average, one hour of chamber treatment cost around 600-1000 Egyptian Pounds ($35-60) in private centers. However, it is not yet covered by health insurance ***[71]*** .

1.4.2 Possible Side Effects, Complications, and Concerns

The side effects of HBOT are based on the physiologic response to a high O_2 pressure environment, and the psychological reaction patients experience in the closed treatment chamber. Despite being one of the safest therapies, there are side effects associated with HBOT as with all medical treatments. The same mechanisms that result in the HBOT's beneficial effects can also cause the known side effects in some patients ***[72]*** , ***[73]*** . Typically, most of HBOT's side effects are mild and self-limited, but, there are risks associated with HBOT that are similar to some diving disorders. Lowering the ambient pressure causes increased gas volume while the opposite is also true [74], ***[75].*** These pressure effects are experienced within physiologic and pathologic air cavities and in the tissues surrounding trapped air inside the body. Of these are several barotraumas in the skull (behind the eardrum ***[76], [77]*** or inside paranasal sinuses ***[77]***), chest (pulmonary barotrauma 'PBT' ***[78]*** or emphysematous bullae ***[79]***), teeth (trapped underneath dental fillings ***[80]***), etc. Middle ear barotrauma (MEB) is widely identified in the peer-reviewed literature where patient education on middle ear clearing, daily monitoring with otoscopy, and proper compression rates are important for prevention ***[79]*** .

Discomfort inside the ears, as a pressure difference develops between the middle ear and the chamber's atmosphere, may be noticed by patients inside the HBOT chamber, which can be readily relieved by ear clearing using the *Valsalva maneuver* or other techniques. Continued pressure increase without equalization may cause tympanic membrane rupture, resulting in severe pain. Also, as the pressure in the chamber increases further, the air may become warmer. Conversely, to reduce the pressure by opening a valve, the pressure falls, which may cause the patient's ears to "squeak" while the pressure inside the ear equalizes with the chamber with a concurrent fall in chamber temperature. This can be prevented by adjusting the speed of pressurization and depressurization to each patient's needs ***[81]*** .

In addition, even though an uncommon and self-limiting side effect, O_2 toxicity seizure is one of the most dreaded side effects of HBOT ***[82]***. Fortunately, it has no long-term complications and usually resolves with the withdrawal of 100% O_2. In such cases, continued HBOT is permissible with maximum allowed pressure adjustment and air breaks. Other HBOT side effects occurring especially in children include claustrophobia and confinement anxiety ***[79]***. Temporarily blurred vision can be caused by swelling of the lens, which usually resolves in two to four weeks ***[83]***, ***[84]***. There are also reports that cataracts may advance with HBOT ***[85]***.

[2] One atmosphere = 101,325 Pa '1,013.25 hPa; 1,013.25 mbar', which is equivalent to 760 mm Hg, 29.9212 inches Mercury (Hg), or 14.696 psi 'pounds per square inch' or 101 kPa).
[3] Henry's Law states that the amount of ideal gas dissolved in solution is directly proportional to its partial pressure ***[4]***.
[4] Boyle's law states that "the absolute pressure exerted by a given mass of an ideal gas is inversely proportional to the volume it occupies if the temperature and amount of gas remain unchanged within a closed system" [74].

2) Methodology

2.1 Study Design

This study is conducted using a cross-sectional survey design to study some indications, contraindications, and some side effects of HBOT in children aged 6 to 10 years (72-120 months).

2.2 Time and Place of Study

The study was conducted during the period from Oct 2018 through Feb 2021 in the Center for Children with Special Needs (an affiliation of the Faculty of Postgraduate Studies of Childhood; Ain Shams University in Cairo, Egypt).

2.3 Study Phases

1. Preparation Phase: This included the following stages:

a) Research and Review of Literature Stage: The objective of this part was to understand the research problem and formulate the research questions. When research keywords and phrases had been identified, the literature review started with a general search of scientific papers using various databases, such as Google Scholar, Google Books, MEDLINE (PubMed), Scopus, ScienceDirect, World of Science, etc. Papers were also found by searching in leading journals, such as Pediatrics, Elsevier, Hyperbaric Oxygen Therapy, etc.

b) Exploratory Study: An exploratory study was carried out to increase the researcher's familiarity with the concepts of work and research setting. This stage lasted three months and was designed to clarify concepts, develop research questions and identify the local resources that might be used in the study.

c) Design of the Study Form: A final interview form and a medical examination sheet were designed.

2. Implementation Phase: This phase lasted about 20 months and included these stages:

a) Pilot Study: A pilot study was carried out on about 10% of the studied sample to estimate the validity of the forms and to examine the parents' acceptability of questions, medical examinations, and investigations.

b) Data Collection and Treatment: Data was collected by completing the designed interview and examination sheets for analysis.

3. Final Evaluation Phase: This phase lasted about 4 months and included the following:

a) Data analysis, management, and interpretation by analytic statistics.

b) Study report was written and edited to its current format.

2.4 Target Population:

The target population of the present study was all the children who visited the study center to receive treatments with HBOT for any indication. All of these children have special needs and are treated with HBOT among other modalities for various conditions.

2.5 Inclusion Criteria

Included in the study are legible children aged 6 to 10 years (72 to 120 months) of both genders that regularly visit the HBOT unit.

2.6 Exclusion Criteria

Excluded from the study were those with:

1. Long-term drug therapy regimens.
2. Ear problems (conductive deafness, eardrum problems).
3. Children with upper or lower respiratory tract infections.
4. Chromosomal or genetic syndromes.

a. Abnormal brain MRI.

b. Depression.

c. Epilepsy.

2.7 Sampling Technique

The sample size for research was based on the total pediatric patients visiting the HBOT unit in the center. The target population yielded 100 respondents as a sample. This sample size constituted nearly 50% of the target population, which was deemed satisfactory for the study. The *Stratified Purposive Sampling technique* was adopted to illustrate the characteristics of particular subgroups of interest.

2.8 Subject and Method

This study was completed in a certain sequence to achieve the objectives of the study. It investigated the prevalence of some indications and some common side effects of hyperbaric oxygen therapy (HBOT) in the studied sample. The final interview sheet and medical examination *cum* investigations form were designed to cover the following:

a. General patients' characteristics (demographics, socioeconomics, and anthropometrics).

b. Prescribed medical indications of HBOT.

c. Side effects and complications of HBOT.

d. Medical examination and investigations.

2.9 Data Collection Tools

1. Interviews:

The interviews are of two types; namely, ***structured*** and ***unstructured [86]*** . The structured interview sheet was designed to accumulate enough information on the following points:

a) Sociodemographic characteristics: Parents' education level, parents' profession, Crowding Index[5] calculation, and parents' and/or patients' satisfaction with the treatment progress. In this study, the household crowding index (HCI)[6] was defined as the total number of co-residents per household, excluding the newborn infant, divided by the total number of rooms, excluding the kitchen and bathrooms. The continuous variable was re-grouped into four distinct categories: 1, 2, 3, and >3.

b) Hyperbaric oxygen therapy (HBOT) related variables: Through asking the following questions to the parents:

- How many sessions has the child taken?
- When was the first session?
- Did they do follow-up during HBOT?
- Did they notice any improvement in their child's health problem?
- Did they notice any side effects of HBOT on their child?
- Was there any doctor or person in the child health center who discussed the importance of HBOT with them?
- Was there any doctor or person in the child health center who discussed the side effects of HBOT with them?
- Did the child take any medications before or during HBOT?
- Did the child take physiotherapy or any other form of therapy before or during HBOT?

2. Medical Examination and Investigations Sheet:

a. **Anthropometric Measurements:** Patient's age, gender, weight at birth and at time of visit, height, and head circumference.
b. **General Examination:** Assessment of general appearance, final diagnosis, therapy modalities, and therapy frequency.
c. Investigations: Relevant labs, Chest X-ray.
d. **Local Examination:** These clinical examinations were done by the researcher to assess the skin, upper limbs, lower limbs, chest, heart, abdomen, nervous system, ENT, and the eyes. In this examination two major tests were performed and quantified:

i. Hamilton Anxiety Rating Scale (HAM-A):

Originally published by Max Hamilton in 1959, it is essentially a clinician-rated psychological evaluation questionnaire used by clinicians to rate the severity of a patient's anxiety [87] for individuals that are already diagnosed with anxiety neurosis [88]. Although it was one of the first anxiety rating scales to be published, the HAM-A remains widely used by clinicians [89]. The scale has a sensitivity of 85.7% and a specificity of 63.5%. Composed of fourteen items, each item is presented in a specific format with some symptoms. Following the item number, the item itself is listed along with a brief description of the criterion (an independent feeling that is related to anxiety) that elaborates on the item and provides specificity to the clinician regarding the appropriate evaluation. To implement the Hamilton Anxiety Rating Scale, the acting clinician proceeds through the fourteen items, evaluating each criterion independently in form of a five-point scale [87].

Adjacent to each item is a five-point scale with a rating of numerals 0 to 4 outlined by a square that indicates a person's anxiety severity where four is the most severe [90]. A rating of 0 indicates that the feeling is not present in the patient, 1 indicates a mild prevalence of the feeling in the patient, 2 indicates

a moderate prevalence, 3 indicates a severe prevalence, and 4 indicates a very severe prevalence of the feeling in the patient. Upon the completion of the evaluation, the clinician compiles a total, composite score based upon the summation of each of the 14 individually rated items. This calculation will yield a comprehensive score in the range of 0 to 56, where a score of 17 or less indicates mild anxiety, a score from 18 to 24 indicates a mild to moderate anxiety and, lastly, a score of 25 to 30 indicates a moderate to severe anxiety severity ***[91].***

ii. ENT Examination.

1) Tympanometry:

Tympanometry is a routinely practiced clinical diagnostic method that has been used to detect the defects in middle ear and eardrum function since the early 1970s, the results of which are plotted on a graph called a tympanogram ***[92]***. Unless the eardrum or middle ear is inflamed, the test is usually rapid and pain-free. In our study, we used the tympanometry grading system in (Table 3).

Table 3: Study Tympanometry Grading System.

1.	Type A	Normal middle ear pressure
2	Type B	Otitis media with effusion
3	Type C	Eustachian tube dysfunction
4	Type $A_{D.}$	Hypermobile tympano-ossicuiar chain
5	Type $A_{S.}$	Decreased tympano-ossicular mobility
6	----------	Test not done

2) Modified Teed Score:

MEB was classified and quantified using the modified Teed score.

2.10 Statistical Analysis:

Data were collected, coded, and then fed to the computer where it was analyzed, and tabulated using the Statistical Package for Social Science (SPSS version 25). The collected data were statistically managed by calculating the Test of Independence or Pearson Chi-Square (χ^2), Analysis of Variance (ANOVA) followed, in some instances, by a Tukey's *post hoc* test for the presence and/or absence of statistically significant differences among the studied variables. The accepted level of significance, *p*-value, was set at ≤ 0.05. Finally, the results were represented in tabular and diagrammatic forms.

2. 11 Ethical Consideration

Ethical considerations were adhered to as per the guidelines and mandates of The Scientific Ethics Committee of the Department of Medical Studies for Children, the Faculty of Postgraduate Studies of Childhood, and the Ain Shams University. Patients and their parents were educated on the purpose of the study. Any patient/guardian whose information was recorded had been notified and agreed to participate by written consent or a verbal assent that their medical information can be used and disclosed for scientific purposes.

[5] *Crowding Index:* According to UN-Habitat, overcrowding occurs if there are more than three people per habitable room ***[95]***.
[6] Household crowding index (HCI) denotes socioeconomically deprived urban communities and a wide range of pathological health outcomes. As a correlate of low parental socioeconomic status, it is associated with longer birth intervals. This association, however, seems to be largely explained by maternal age and parity ***[96]***.

3) Results

3.1 Demographic Trends

The ages of the study participants ranged from 72 to 120 months (6-10 years) with a mean ± SD of 89.2 ± 16.7 months (Fig. 1). As for participants' gender, most of children (N=69; 69.0%) were males and (N=31; 31.0%) were females (Fig. 2) (See Supplement: Table 1 & 2).

3.2 Anthropometric Characteristics

Most children (N=59; 59%) were underweight while (N=33; 33%) were normal and only (N=8; 8%) were overweight. In addition, stunted children constituted (N=61; 61%) and those with microcephaly (N=58; 58%) (Fig. 3) (See Supplement: Table 3 & 4).

3.3 Socioeconomic Characteristics

Studying the socioeconomic characteristics of the participants' families included the parents' education level, occupation, and the family housing crowding index, the results of which showed the data depicted in figures 4, 5 & 6 (See Supplement: Tables 5 & 6).

3.4 Clinical Attributes

Results showed that as for the final diagnosis, (N=38; 38%) of cases had LDs, (N=36; 36%) of cases had CP, (N=20; 20%) had ASD, (N=4; 4%) had ADHD, and (N=2; 2%) of cases were treated for wounds. As regards receiving treatment, nearly one-third of each; (N=32; 32%) received physiotherapy, and (N=29; 29%) received development therapy. In addition, (N=23; 23%) received speech therapy, and (N=16; 16%)

received pharmaceutical therapy. The number of sessions of those therapy modalities ranged from 3 to 57 with a mean ± SD of 22 ± 13.3 sessions (Fig. 7) (See Supplement: Tables 7 & 8).

3.5 Tests and Investigations

Medical examinations and investigations revealed that on performing tympanometry most children (67%) had normal middle ear pressure. Only 6% demonstrated otitis media with effusion, 6% had decreased tympano-ossicular mobility, 5% had hypermobile tympanoossicular chain, and 4% had Eustachian tube dysfunction. On calculating the modified Teed Score, more than one-half of children (56%) showed normal ear pressure, about one quarter (24%) showed TM injection or retraction, 10% had slightly hemorrhagic eardrum, 3% grossly hemorrhagic, 1% had tympanum, and 6% had TM perforation. According to the quantitative HAM-A scale, the majority of children had mild anxiety (98%) while only 2% had moderate to severe anxiety. Even though the scores fell within the range of (0-46), the Mean ± SD of the HAM-A score was 3.1 ± 6.1. As to Parents' satisfaction levels, 26% were satisfied, and 21% were highly satisfied; but, more than one-third (35%) were neutral and 18% were not satisfied (Fig. 8) (See Supplement: Tables 9 & 10). These responses may be biased due to parents' emotional status at the time of the interview or their educational or intelligence background.

3.6 Dependent Variables Relationships

In the detailed analysis of all variables scrutinized in the study; especially, between the investigative tests done to measure side effects and the elements affecting them, not many statistically significant relationships were detected. But, by employing Pearson Chi-Square (χ^2), several inter-relationships of statistical significance were found amongst variables denoted by the *p*-values (Table 4).

Table 4: Detailed p-values of all related variables in the study.

Variables	Tympanometry	Teed Score	HAM-A Score	Parents Satisfaction	Diagnosis	No of Sessions	Age
Tympanometry		**0.000**	**0.000**	0.549	0.094	**0.014**	0.282
Teed Score	**0.000**		0.393	0.522	**0.029**	0.111	0.194
HAM-A Score	**0.000**	0.393		0.522	**0.016**	**0.003**	0.218
Parents' Satisfaction	0.549	0.522	0.522		**0.019**	**0.000**	**0.011**
Diagnosis	0.094	**0.029**	**0.016**	**0.019**		0.821	**0.001**
No. of Sessions	0.098	0.820	**0.003**	**0.000**	0.821		0.276
Age	0.282	0.194	0.218	**0.011**	**0.001**	0.276	

p-values of significance calculated by Test of Independence or Pearson Chi-Square (χ^2) are shaded in light blue where the *p*-value ≤0.05.

3.7 Tympanometry Test

As regards tympanometry, Chi-Square (χ^2) demonstrated statistically significant relationships between types of tympanometry and both Teed and HAM-A Scores where *p*-value= 0.00. By ANOVA, there were several statistically significant relationships between groups and within groups (Table 5). A Tukey's *post hoc* test on Teed and HAM-A Scores showed that between groups the significant relationship escalated

from one item of Teed Score to the other with tympanometry as follows: Type B > Type A_D > Test Not Done > Type A_S > Type C > Type A. In addition, as to HAM-A Score, the relationship with tympanometry was as follows: Type A_D > Type B > Type A > Test Not Done > Type C > Type A_S.

Table 5: Study of Significance by ANOVA for Tympanometry Test with Teed Score and HAM-A Score.

ANOVA Analysis for Tympanometry				**F**	**Sig.**
Teed Score	***Between Groups***	(Combined)		37.207	0.000
		Linear Term	Weighted	10.041	0.002
			Unweighted	9.806	0.002
		Deviation		43.999	0.000
HAM-A Score	***Between Groups***	(Combined)		10.425	0.000
		Deviation		12.516	0.000

3.8 Parents' Satisfaction

As regards parents' satisfaction, Chi-Square (χ^2) demonstrated statistically significant relationships between grades of satisfaction and the age of patients, diagnoses, and the number of therapeutic sessions where (χ^2) *p*-values= 0.011, 0.019, and 0.000 respectively. As for the number of sessions by ANOVA analysis (followed by Tukey's *post hoc* test), the satisfaction degree between groups was graded as: Highly Satisfied > Satisfied > Unsatisfied > Neutral.

3.9 HAM-A Score

A more detailed study of each of the 14 items that constitute the Hamilton Anxiety Score (HAM-A) showed that, in general, most patients did not show any symptoms of anxiety and that more than one-half did not show any at all (Figures 9 & 10) (See Supplement: Tables 11 & 12).

a. ***HAM-A Score with Demographic, Anthropometric, and Socioeconomic Characteristics:*** No statistically significant relationships (See Supplement: Table 13 & 14).
b. ***HAM-A Score with Clinical Attributes:*** A statistically significant relationship was found with diagnosis. The two cases of the moderate-severe form of anxiety were CP and ADHD (Fig. 11) (See Supplement: Table 15).
c. ***HAM-A Score with Other Tests and Investigations:*** As to the other tests and investigations for tympanometry, Teed Score, and Parents' Satisfaction with HAM-A, a statistically significant relationship was found only between HAM-A score and Tympanometry (See Supplement: Table 16).

4) Discussion

This study targeted 100 (nearly 50%) legible pediatric patients of all patients population visiting the study center for HBOT at the time of the study. The participants were all pediatric patients, mostly with special needs (age range: 72 to 120 months, of mixed genders) and their parents/guardians who were included in the study based on the study methodology's inclusion and exclusion criteria using a cross-sectional survey design. The study sample was withdrawn using the stratified purposeful sampling technique, and, therefore, there was a lack of homogeneity in the distribution of variables but we could only withdraw from available legible participants. The response rate to the study interview form was 100 (100%). In our study, receipt of well-care comprehensive assessment was tracked by the study system as a measure of healthcare quality [93], [94]. To start with, we aimed at establishing a profile of the pediatric patients visiting the HBOT unit of our study center, describing the demographic characteristics of the patients and the epidemiology of their presentations.

The study sought to gather information on various aspects of the respondents' background in terms of socioeconomic characteristics including Parents' Education Level and Occupation, the Housing Crowding Index (to estimate the Living Conditions), and their Level of Satisfaction with the Progress of their Child Therapy. Then, the respondents were asked to indicate the various diseases their child was being treated for and with which modalities in conjunction with HBOT. The most important tools used were the main interview form, which included the parents' questionnaire as well as the medical examination, and the investigations sheet to record the demographic attributes and anthropometric measurements and to evaluate the patients' general health status. The researcher clinically examined the skin, upper limbs, lower limbs, chest, heart, abdomen, nervous system, and eyes. In addition, general appearance, final case diagnosis, and therapy modalities/frequency were noted. In the special systematic examination, two major tests were performed and quantified: the Hamilton Anxiety Score and a thorough Ear, Nose, and Throat examination, which included tympanometry and a modified Teed Score evaluation and analysis of their results with to other study attributes. For some patients, some labs and chest X-ray examinations were performed but not included in the study.

Demographically, the results showed more encounters with male patients (n = 69; 69%) than female patients (n = 31; 31%), which is not a homogenous distribution of both genders in the sample, but we included all legible patients in the targeted age range. There were several age groups between 72 months to 120 months of age (6–10 years) (Range = 48; Min = 72 months; Max = 120 months; Mean ± Standard Deviation = 89.17 ± 16.74 months). The largest age group was of 6–7 years of age (n = 56; 56%) followed by 9–10 years group (n = 18; 18%), 8–9 years (n = 14; 14%) and 7–8 years (n = 12, 12%).

In addition, we studied the anthropometric measurements of the patients to classify them clinically. Results showed that the majority were in the underweight range (n = 59; 59%) followed by the normal-weighted children who constituted one-third of the sample (n = 33; 33%) and lastly, only a few were overweight (n = 8; 8%). As for height, the majority were stunted (n = 61; 61%) and the normal (n = 39; 39%). Also, as regards head circumference, it was appalling to find the majority had microcephaly (n = 58; 58%)

and those with normal head circumference constituted (n = 42; 42%). No macrocephaly cases were found. We can deduce that these prevalent off-normal anthropometrics are commensurate with children with special needs that visit this particular center for treatments and do not represent the normal pediatric population in Cairo.

Socioeconomically, the participants showed some interesting facts. As for the father's education level, the results indicated the highest frequency for low education (n = 30) followed by high education (n = 26), illiteracy (n = 25), and lastly, average education (n = 19). Mother's education was not very different; results indicated a high frequency of low education (n = 36) followed by illiteracy (n = 26), high education (n = 25), and lastly, average education (n = 13). Father's occupation categories ranged among high-scale profession that constituted a majority (n = 45), clerical job (n = 19), merchant (n = 16), farmer (n = 12), and lastly, manual labor (n = 8). On the other hand, the mother's occupation ranged only between working (n = 40), and housewife (n = 60). To draw deeper relationships between disease and socioeconomic attributes, it was only prudent to calculate the housing crowding index. Overall, it was high in all instances reaching 2 (n = 41), 3 (n = 49), and 4 (n = 10) conforming to other previous research [95], [96].

Withdrawn from a population of children with special needs, our study sample revealed that the highest propensities among patients to seek HBOT were for Learning Disabilities 'LD' (n = 38; 38%) followed by Cerebral Palsy 'CP' (n = 36; 36%), and at third rank, Autism Spectrum Disorders 'ASD' (n = 20; 20%). The remaining few cases were divided between ADHD (n = 4; 4%), and Wounds (n = 2; 2%). Although we wanted to extensively study the effects and side effects of HBOT on the wound cases, the population we had to withdraw from did not offer such an opportunity. The analysis involved the examination of the portfolios of the 100 pediatric patients who completed a total of 2203 therapeutic sessions of different modalities including HBOT during the period from Jan 2019 through Dec 2020 (Min = 3 sessions, Max = 57 sessions, Range = 54 sessions; Mean ± Standard Deviation = 22.03 ± 13.26 sessions). In conjunction with HBO_2 treatments, almost one third were treated with physiotherapy (n = 32; 32%) followed by developmental therapy (n = 29; 29%), conversation speech therapy (n = 23; 23%) and lastly pharmaceutical therapy (n = 16; 16%). In addition, during the study duration, the highest frequency of patients had 11–20 total sessions (n = 36) followed by those who had 1–10 total sessions (n = 26), 31–40 total sessions (n = 15), 21–30 total sessions (n = 13), 41–50 total sessions (n = 6), and lastly, those who had more than 50 total sessions (n = 4).

In our search to quantify the side effects of HBOT in our sample and to investigate their significant relationships with the study variables, we resorted to local ENT examination and patients' anxiety severity measurement. Because MEB is the most common of HBOT side effects, the tympanometry test was a test in place here to evaluate the middle ear condition in the patients receiving HBOT. In our sample, the test could not be performed for 12 patients but of the 88 left, 78 were diagnosed with Type A: Normal middle ear pressure of which 5 were of Type A_D (Hypermobile tympano-ossicular chain) and 6 with Type A_S (Decreased tympano-ossicular mobility). Only 6 cases presented with Type B (Otitis media with effusion) and 4 with Type C (Eustachian tube dysfunction). Similarly, based on the middle ear examination, the modified Teed score demonstrated suffering from a few side effects. Of the 100 cases,

more than half (n = 56; 56%) presented with grade 0: Symptoms with no ontological signs of trauma (Normal examination). About one quarter (n = 24; 24%) showed grade 1: Diffuse redness (injection) and retraction of the TM. The remaining one-fifth was distributed over those with grade 2: Slight hemorrhage within the tympanic membrane (n = 10; 10%), grade 3: Grossly hemorrhagic TM (n = 3; 3%), grade 4: Dark and slightly bulging TM due to free blood in the middle ear or hemotympanum (n = 1; 1%) and grade 5: Free hemorrhage into the middle ear or TM perforation with blood visible in the external auditory canal (n = 6; 6%). Therefore, the findings corroborated other findings by previous studies which postulated that MEB can be avoided and its incidence reduced with adequate patient education, training, and assistance through active coaching during compression [63], [97], topical medications, and (in less common circumstances) relatively benign surgical intervention [79].

In addition, as claustrophobia appears to be present in about 2% of the general patient population and may cause some degree of confinement anxiety [98] even in a multiplace chamber, we employed Hamilton Anxiety Score (HAM-A Score) to study anxiety symptoms severity in our study's patients. The findings against all 14 axes of the score were very interesting. The majority showed almost no anxiety symptoms (score range = 82–96); and in total, only two patients expressed moderate to severe symptoms (25 to 30) and the remaining 98 fell within grade 1: mild prevalence of the feeling in the patient. This can be easily understood when we mention that the mono-place chambers in the center were made of glass where the partially-sedated child can see outside the chamber and as the parent sits beside the unit and can be visualized throughout the session duration through the glass, a factor that is highly reassuring for the child. The results agree with the literature where the incidence of confinement anxiety in monoplace chambers is reported at 8 events per 10,000 treatments and that mild confinement anxiety is easily controlled with sedation before treatments so that individuals may continue to receive daily HBOT [99]. Preventive measures with adequate patient history, patient education, reassurance, and coaching are also among the most effective means of anticipating episodes of claustrophobia or anxiety and treating them effectively before HBOT [79].

To complete the analytical investigations, we resorted to analyzing parents' satisfaction with the progress of their children's treatment with HBOT both qualitatively and quantitatively. Almost one-half were satisfied with the progress of which 21 were highly satisfied and 26 satisfied. The neutral responses of slightly more than one-third (n = 35; 35%) may have been due to a lack of education or due to parents' apprehension or worry during the time of the interview. However, the unsatisfied group constituted n = 18 (18%).

It was beneficial for our study to investigate the relations between some responses and/or test outcomes and patients' attributes such as their demographic, socioeconomic, anthropometric, and clinical characteristics. The analysis confirmed several significant relationships between some variables. As regards tympanometry, Chi-Square (χ^2) test demonstrated statistically significant relationships between types of tympanometry and both Teed and HAM-A Scores where (χ^2) *p*-value was 0.000 ($p < 0.05$). ANOVA (with a Tukey's *post hoc* test) on Teed and HAM-A Scores results showed that between groups, the significant relationship escalated from one item of Teed Score to the other with tympanometry, in tandem,

as follows: Type B > Type A_D > Test Not Done > Type A_S > Type C > Type A. In addition, as to HAM-A Score, the relationship went as follows: Type A_D > Type B > Type A > Test Not Done > Type C > Type A_S. Similarly, it was natural to find a significant relationship between modified Teed Score and Diagnoses ($p = 0.029 < 0.05$). In addition, the HAM-A Score had statistically significant relationships with Tympanometry grades ($p = 0.000 < 0.05$), Diagnoses ($p = 0.016 < 0.05$) and Number of sessions ($p = 0.003 < 0.05$).

As regards Parents' Satisfaction, the Chi-Square (χ^2) test demonstrated statistically significant relationships between grades of satisfaction on one side and Age of Patients, Diagnoses, and Number of Therapeutic Sessions on the other side where (χ^2) *p*-values were 0.011, 0.019 and 0.000, respectively. ANOVA analysis (followed by Tukey's *post hoc* test) gave the following results between groups with the number of sessions: Highly Satisfied > Satisfied > Unsatisfied > Neutral. Age of patients was statistically significant with Diagnoses ($p = 0.001 < 0.05$) and Parents' Satisfaction ($p = 0.011 < 0.05$). From the same results above, Diagnosis shared statistically significant relationships with all Patient's Age ranges ($p = 0.001 < 0.05$), modified Teed Score ($p = 0.029 < 0.05$), HAM-A Score ($p = 0.016 < 0.05$), and Parents' Satisfaction ($p = 0.019 < 0.05$). In the study, patients never complained of O_2 toxicity after treatments. Reviewing chest X-rays of the patients did not reveal any pulmonary complications apart from the normal seasonal or infectious inflammations. In the same setting, history and perfunctory eye examination showed no relevant ophthalmological side effects or complications, or dental complaints.

5) Conclusion

HBOT is one of the safest curative modalities used today even though its primary and secondary effects result in its benefits as well as its side effects. One of the most common side effects identified in the peer-reviewed literature is MEB, which is typically mild and self-limited and can be prevented by patient instruction on middle ear clearing, daily monitoring with an otoscopic examination, and appropriate compression rates. Claustrophobia or confinement anxiety in monoplace chambers is another side effect of HBOT, but, it is generally mild and anxiety is easily controlled with sedation before treatments so that individuals may continue to receive daily HBOT. Preventive measures with adequate patient history, patient education, reassurance, and coaching are the most effective means of anticipating episodes of claustrophobia and treating them effectively before HBOT.

6) Recommendations

Further research can explore ways of effectively identifying appropriate HBOT indications and unfavorable side effects beyond the scope of this study. MEB can be prevented by ongoing teaching of middle ear clearing techniques and appropriate compression rates. Claustrophobia may be managed with coaching and anxiolytic medications. Intolerance of a monoplace chamber may warrant referral to the closest multiplace chamber facility. PBT is unlikely and can be avoided with appropriate pretreatment screening. Providers should monitor the degree of change during treatment to assure safety and instruct patients to avoid a new permanent prescription until at least 8 weeks after treatment is completed.

Certain precautions should be taken, and the involvement of multidisciplinary pediatric specialists and/or consultants in the prescription of HBOT is important when treating children, especially those with special needs.

Declarations

Funding: The present study was financially supported solely by the author.

Conflicts of Interest: The author declares no conflicts of interest.

Institutional Review Board Statement: The study was conducted according to the guidelines and approved by The Scientific Ethics Committee of the Department of Medical Studies for Children, the Faculty of Postgraduate Studies of Childhood, and the Ain Shams University.

Informed Consent Statement: The author reviewed and agreed to the published version of the manuscript.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Abbreviations

ADHD	attention-deficit hyperactive disorder
AGE	arterial gas embolism
ASD	autism spectrum disorder
ATA	atmospheres absolute
ATP	adenosine triphosphates
CNS	central nervous system
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
CP	cerebral palsy
DBP	diastolic blood pressure
EF	ejection fraction
ET	Eustachian tube
HAM-A	Hamilton Anxiety Score
HBO_2	Hyperbaric oxygen
HBOT	hyperbaric oxygen therapy
IGF-1	insulin-like growth factor
LD	Learning disability
MEB	middle ear barotrauma
NO	nitric oxide
O_2	Oxygen molecule
$ONOO^-$	peroxynitrite
PaO_2	partial pressure of oxygen in arterial blood
PBT	pulmonary barotrauma
pO_2	partial pressure of oxygen
PTX	pneumothorax
RBC	Red blood cell
ROS	reactive oxygen species
SBP	systolic blood pressure

TM	tympanic membrane
VEGF	vascular endothelial growth factor
UHMS	The Undersea and Hyperbaric Medical Society

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Figures

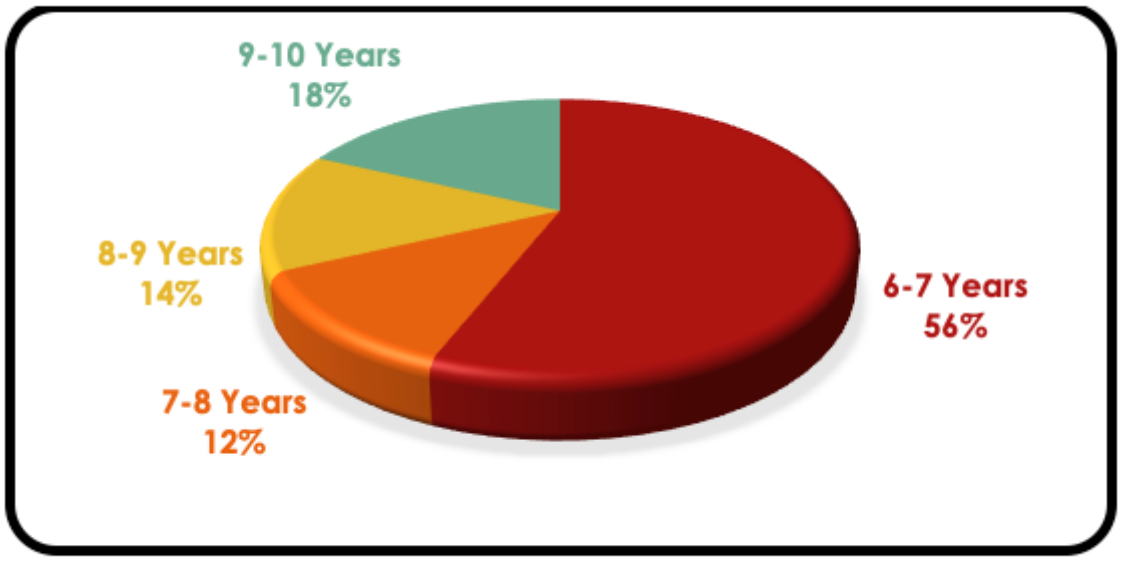

Figure 1: Patients' Age Distribution in Years.

Figure 1

See image above for figure legend.

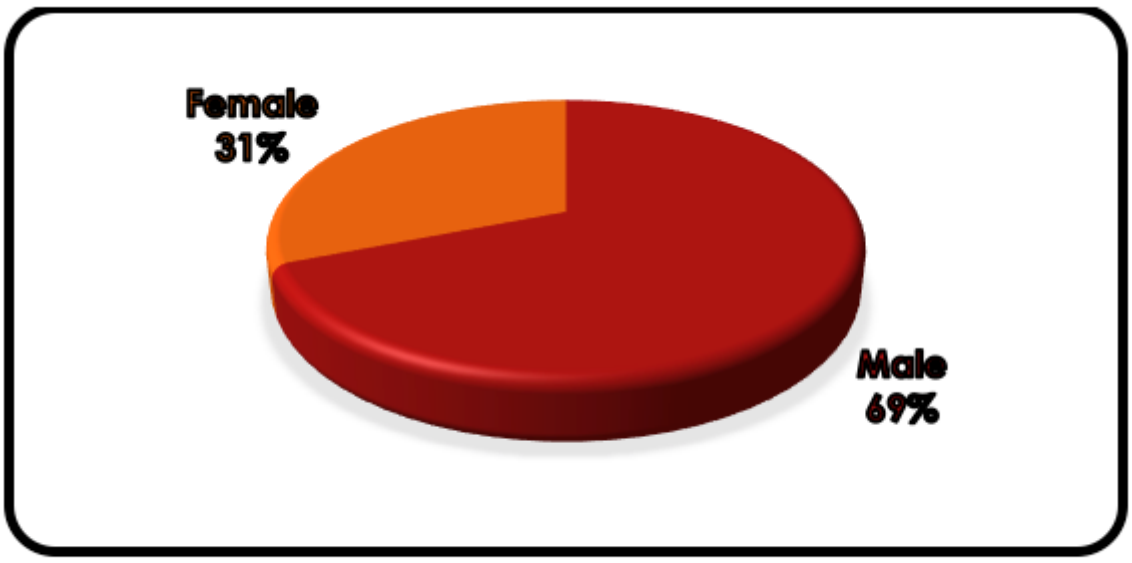

Figure 2: Patients' Gender Distribution.

Figure 2

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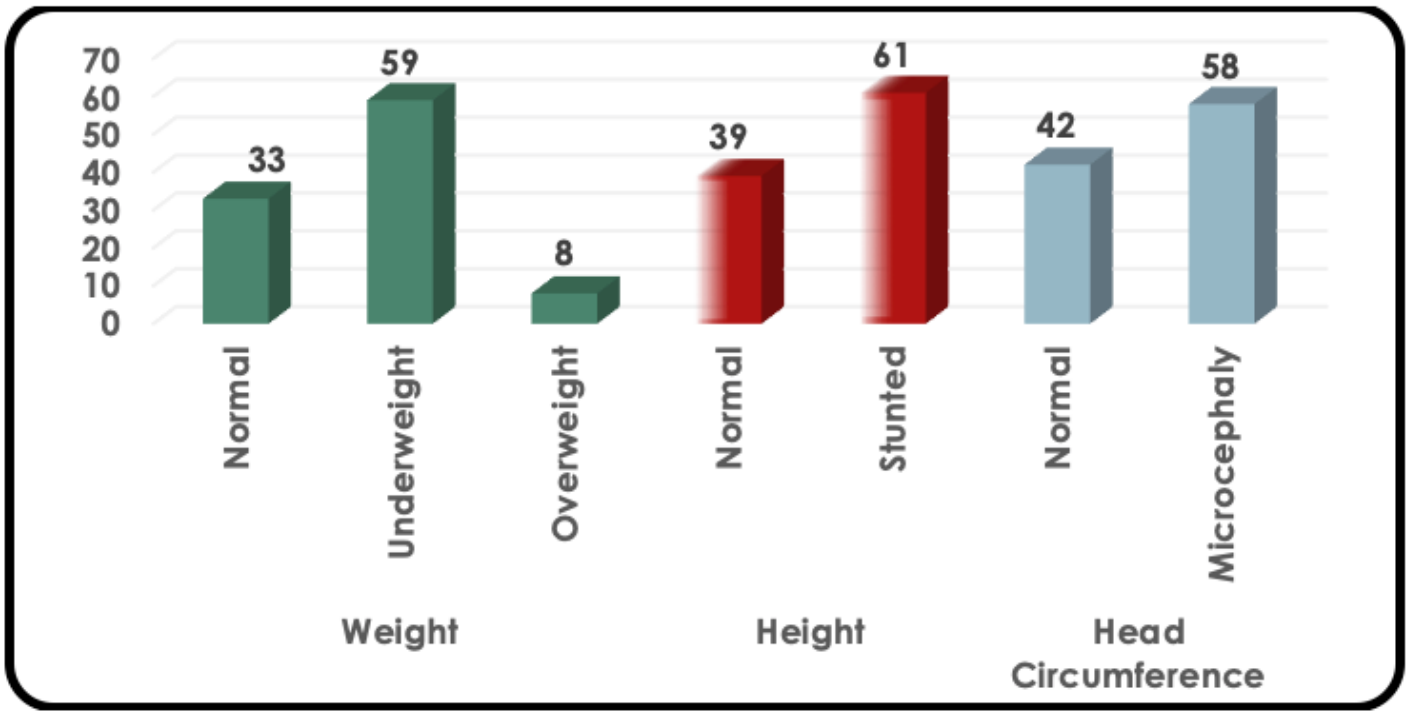

Figure 3: Patients' Anthropometric Characteristics.

Figure 3

See image above for figure legend.

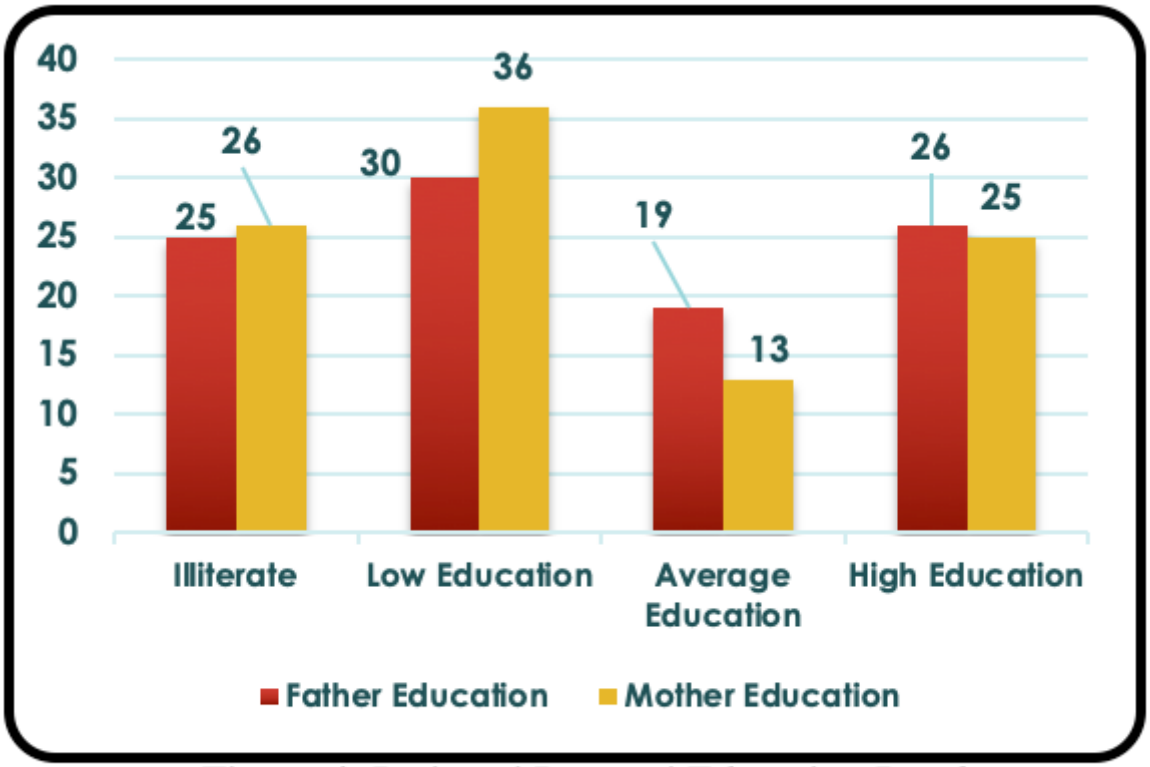

Figure 4: Patients' Parents' Education Level.

Figure 4

See image above for figure legend.

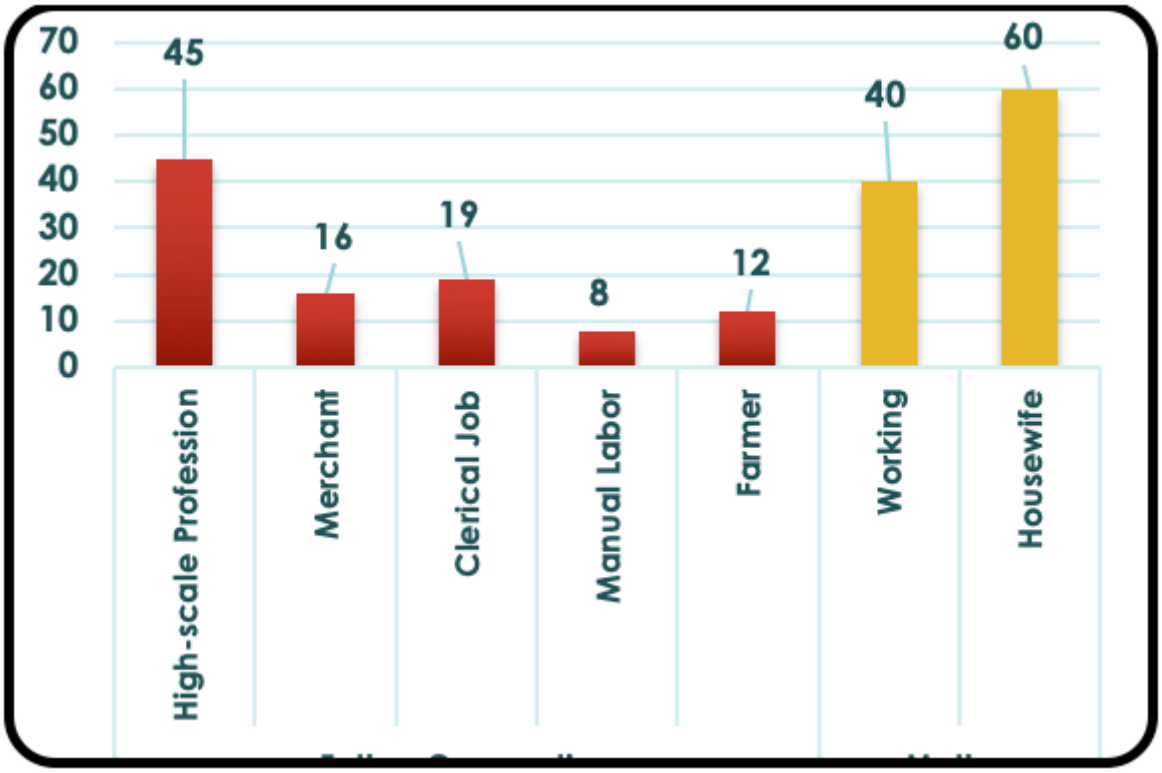

Figure 5: Patients' Parents' Occupation.

Figure 5

See image above for figure legend.

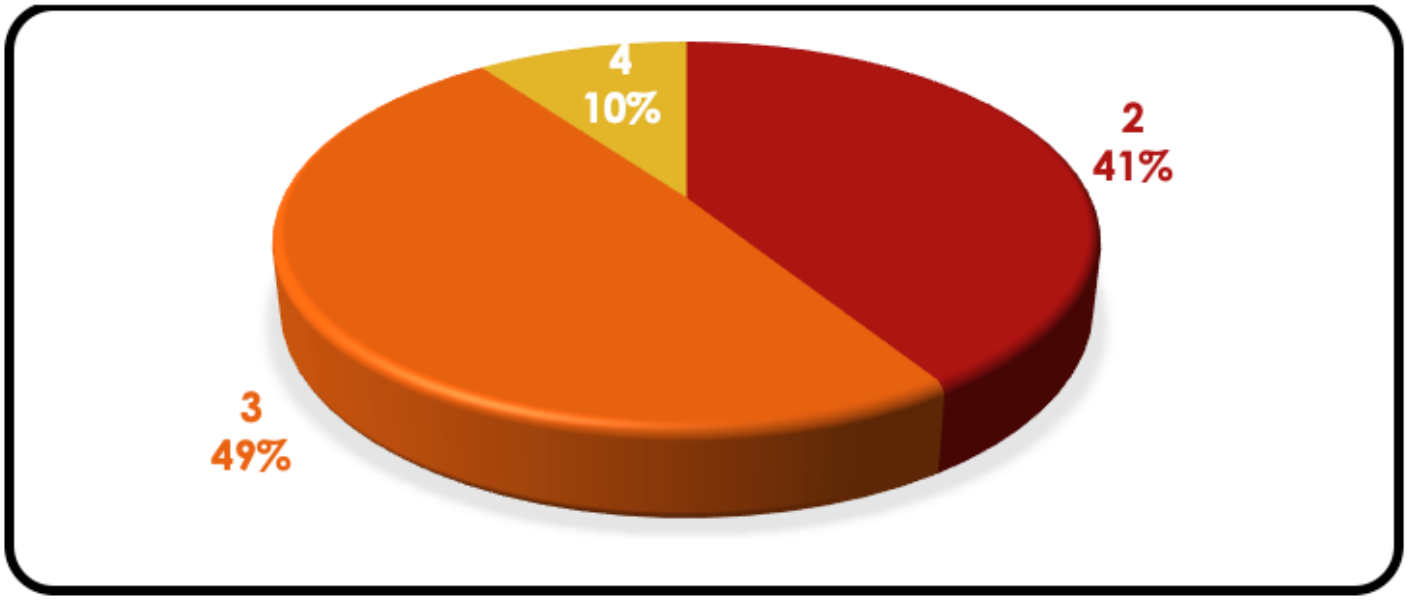

Figure 6: Patients' Family Housing Crowding Index.

Figure 6

See image above for figure legend.

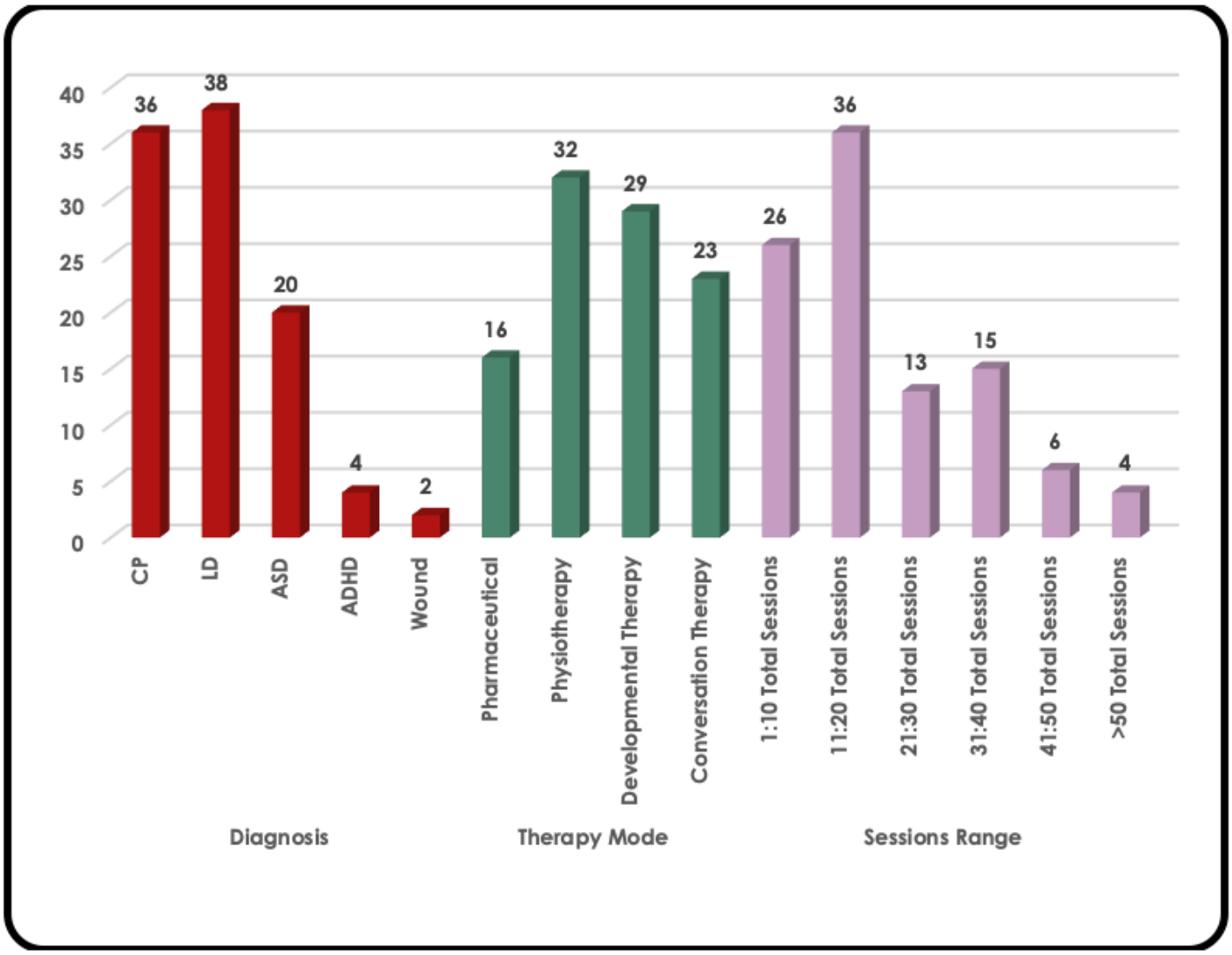

Figure 7: Participants' Clinical Attributes.

Figure 7

See image above for figure legend.

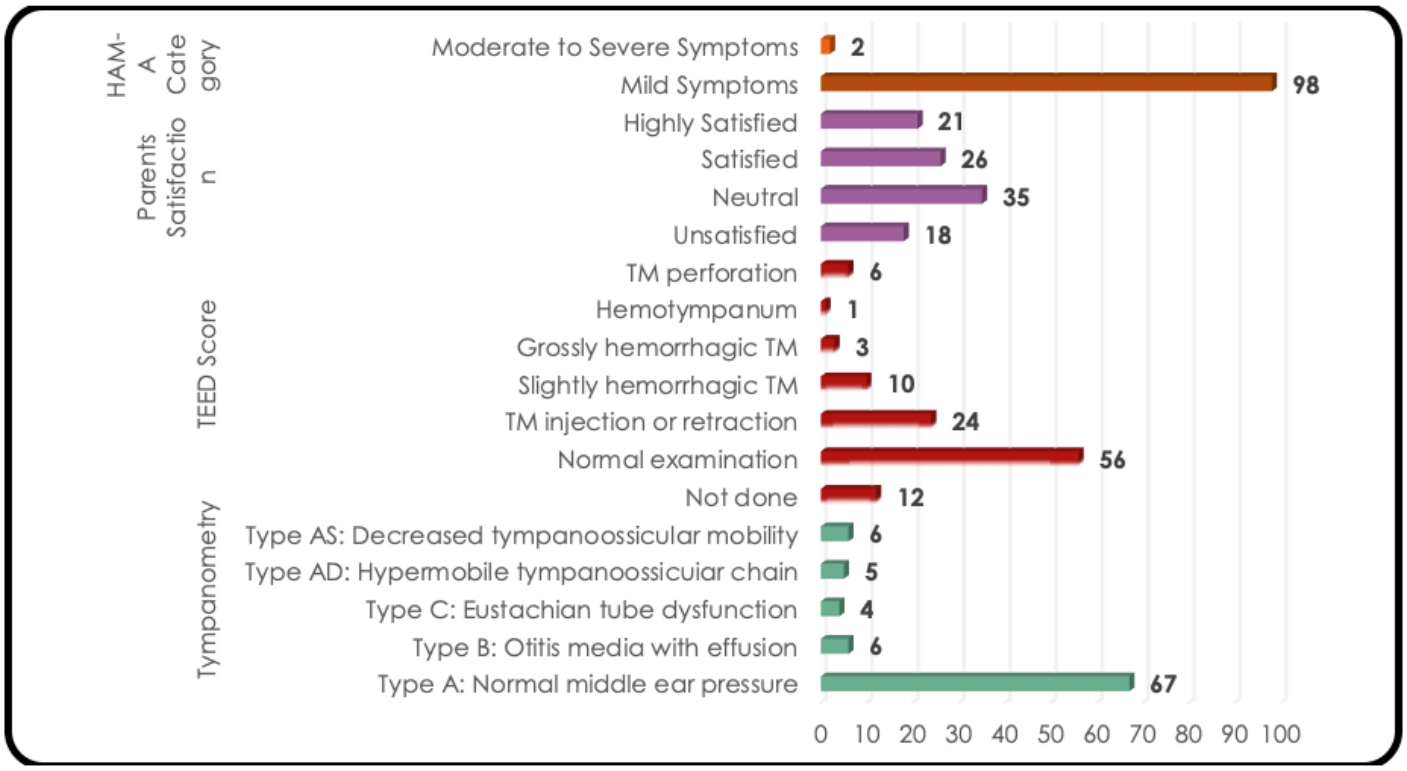

Figure 8: Patients' Tests and Investigations Findings.

Figure 8

See image above for figure legend.

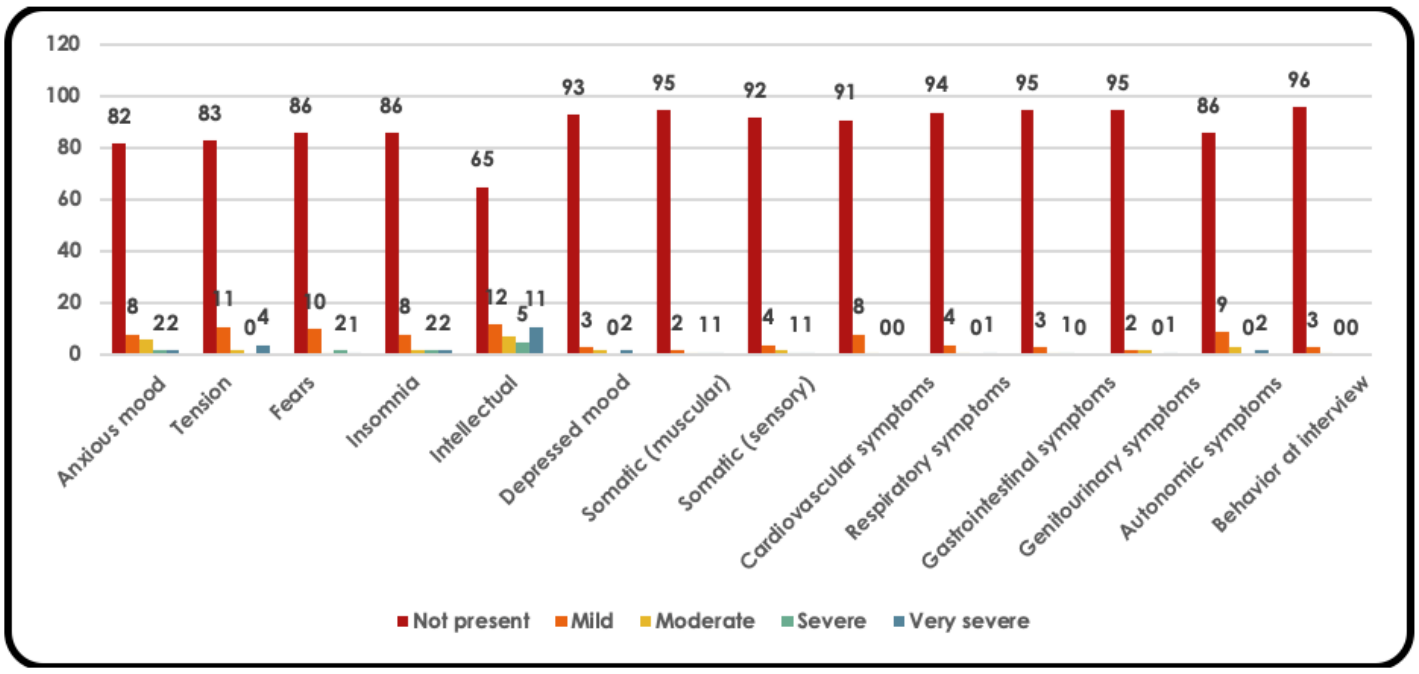

Figure 9: HAM-A Score Degrees of Severity to Number of Patients.

Figure 9

See image above for figure legend.

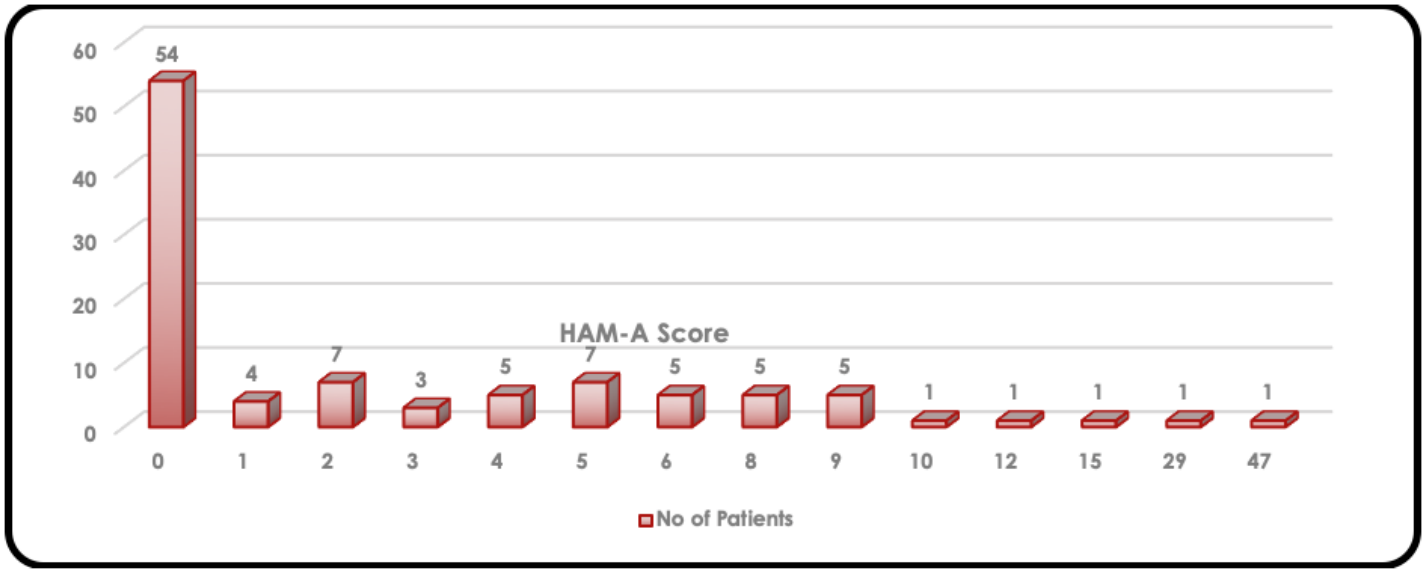

Figure 10: Total HAM-A Score to Number of Patients.

Figure 10

See image above for figure legend.

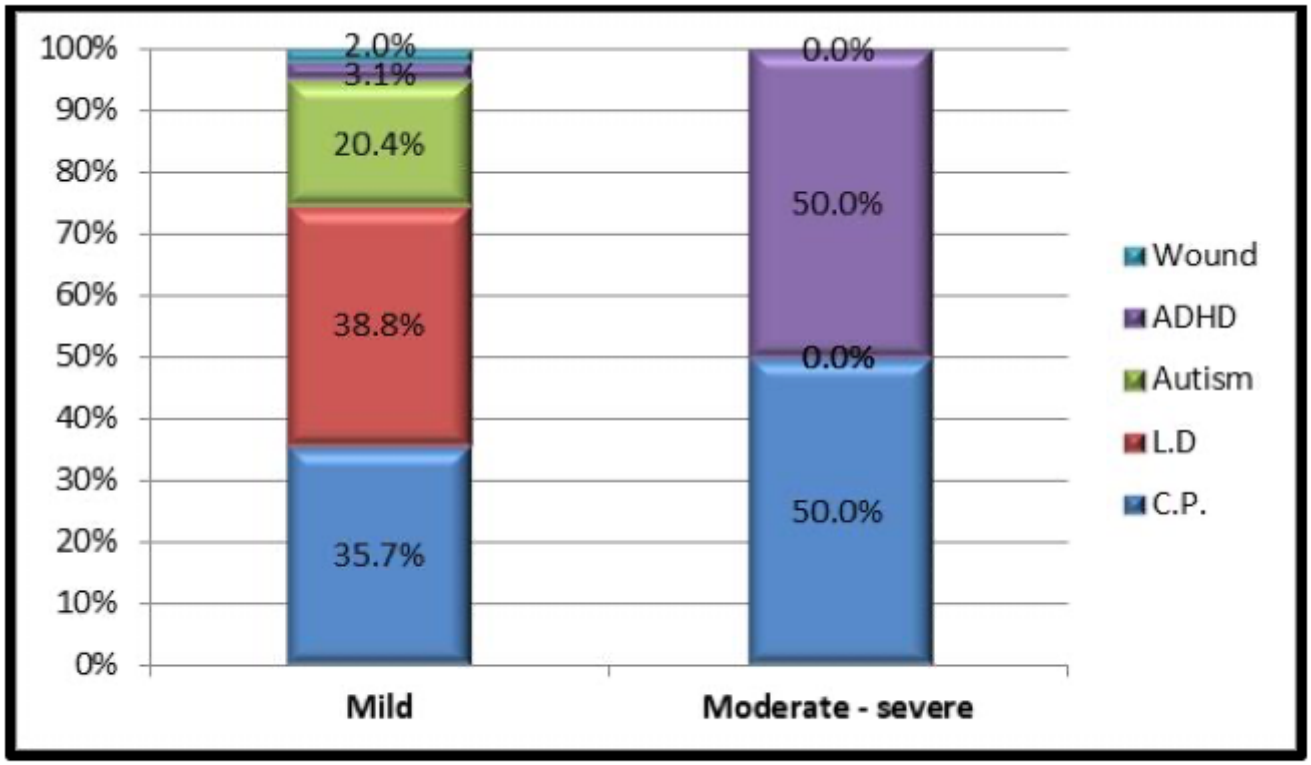

Figure 11: HAM-A Score with Diagnosis.

Figure 11

See image above for figure legend.

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