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Policy Review

Predicting hyperbaric oxygen therapy success using the decision tree approach

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A R T I C L E I N F O

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Plastic and reconstructive surgery

A B S T R A C T

Introduction: Hyperbaric oxygen therapy (HBOT), a procedure that involves the patient inhaling 100% oxygen gas under pressure, is currently used as an adjunctive treatment option for certain inflammatory conditions. HBOT can improve wound healing by increasing the rate of angiogenesis in injured tissue by increasing levels of vascular endothelial growth factor (VEGF). VEGF causes re-epithelialization, the migration of endothelial cells, and the formation of granulation tissue, which are involved in the wound healing process.
Methods: This study contains secondary data analyses of information previously collected in two separate studies, each concerning the effects of HBOT on diabetic foot ulcers and crush injury fractures at Prof. Dr. R. D. Kandou Hospital Manado and Siloam Hospital Manado from 2019 to early 2020.
Results: Based on the classification tree analysis, the predictors of HBOT success were leukocytes level (34%), platelet count (32%), and age (26%). The conditional inference tree analysis also indicated significant leukocyte levels, age, and platelet counts ($p < 0.001$), with which the interpretation of these results was the same as the classification tree analysis method. The results obtained from the random forest analysis revealed that the mean value of Gini reduction for leukocytes (207.3), platelets (110.2), age (97.9), and hemoglobin (57.9) can be used as indicators of successful HBOT. These three methods support that age, leukocytes, and platelets are determinants of HBOT success, while hemoglobin levels were only significant in one analysis method. Therefore, a new, proposed algorithm containing these factors was assembled from the results of this study.
Conclusion: HBOT cannot be separated from specific variables that contribute to and can predict its success.

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1. Introduction

Hyperbaric oxygen therapy (HBOT) involves a patient inhaling 100% oxygen gas under pressure and is currently used as adjunctive therapy for bacterial infections. The antimicrobial effect of HBOT is a reaction to the formation of reactive oxygen species (ROS). Its application to infection management promotes faster healing [1]. HBOT is also believed to bolster the immune system and acts synergistically with several anti-microbial agents. HBOT is useful against various infections, especially deep and chronic infections such as necrotizing fasciitis, osteomyelitis, soft tissue infections, and infective endocarditis [2–4]. The anti-inflammatory properties of HBOT indicate that it can play a major role in reducing tissue damage and halting the progression of infection [5,6].

The incidence and complications of diseases with impaired wound healing are still common in the clinical world. The global prevalence of diabetic foot ulcers is 6.3% and the prevalence in men is higher than in women [7]. Acute peripheral ischemia that threatens leg viability has an incidence of 9–16 of 100,000 people per year for the lower limbs and up to 1–3 cases of 100,000 people per year for the upper limbs [8]. Gangrene gas was found in 110 patients studied in a retrospective cohort, which resulted in 85 major amputations [9]. HBOT is also used in trauma cases, especially in severe tissue damage, such as crush injuries. HBOT can save limb injuries from progressing to the threat of amputation by providing oxygenation to ischemic tissues.

The effectiveness of wound healing with HBOT has been reported in several studies [10,11]. HBOT improves wound healing by increasing the rate of angiogenesis in injured tissues through increasing levels of vascular endothelial growth factor (VEGF). VEGF induces the re-epithelialization and migration of endothelial cells and the formation of granulated tissue, which are essential stages in the wound healing process [11,12].

The secondary mechanisms of action of HBOT include vasoconstriction, angiogenesis, fibroblast proliferation, oxidative leukocyte elimination, toxin inhibition, and synergism with antibiotics [13]. Under normal circumstances, tissue hypoxia causes due to the compensatory mechanism of increased microvascular blood flow [14]. However, adequate oxygen levels are required for tissue repair and HBOT plays an important role in this mechanism [15].

HBOT increases the production of reactive oxygen species (ROS) from mitochondria, as well as reactive nitrogen species (RNS). Both ROS and RNS are involved in the transduction cascade that produces Pro-inflammatory factors, cytokines, and hormones. The RNS cascade stimulates endothelial nitric oxide synthase (eNOS), which produces nitric oxide (NO), a signal required for the activation and recruitment of endothelial progenitor cells (EPCs) [16]. ROS oxidize protein and membrane lipids, damages DNA, and inhibits bacterial metabolism [1,16]. Moreover, HBOT inhibits toxins produced by *Clostridium* bacteria and increases the working potential of antibiotics that use oxygen to transport between cell membranes such as fluoroquinolones, amphotericin B, and aminoglycosides [1]. The mechanism of the ROS and RNS is described in more detail in the following Fig. 1.

HBOT as an adjuvant or complementary therapy is widely applied today [10,11,17–19]. Several studies demonstrate the effectiveness of HBOT in wound healing and inflammation [4,12,20,21].

However, to our knowledge, no study has been conducted on developing an algorithm to determine the need for HBOT or predict its success. This study aims to develop an algorithm that can be used to inform the implementation of HBOT based on the decision tree approach.

2. Methods

2.1. Study design

This study is a secondary data analysis of information previously collected in two separate studies, each concerning the effects of HBOT on diabetic foot ulcers [21] and crush injury fractures [12]. This research is structured to analyze the HBOT approach from a new perspective, specifically, the development of an algorithm to determine therapy based on the algorithm's predictive ability using a decision tree analysis.

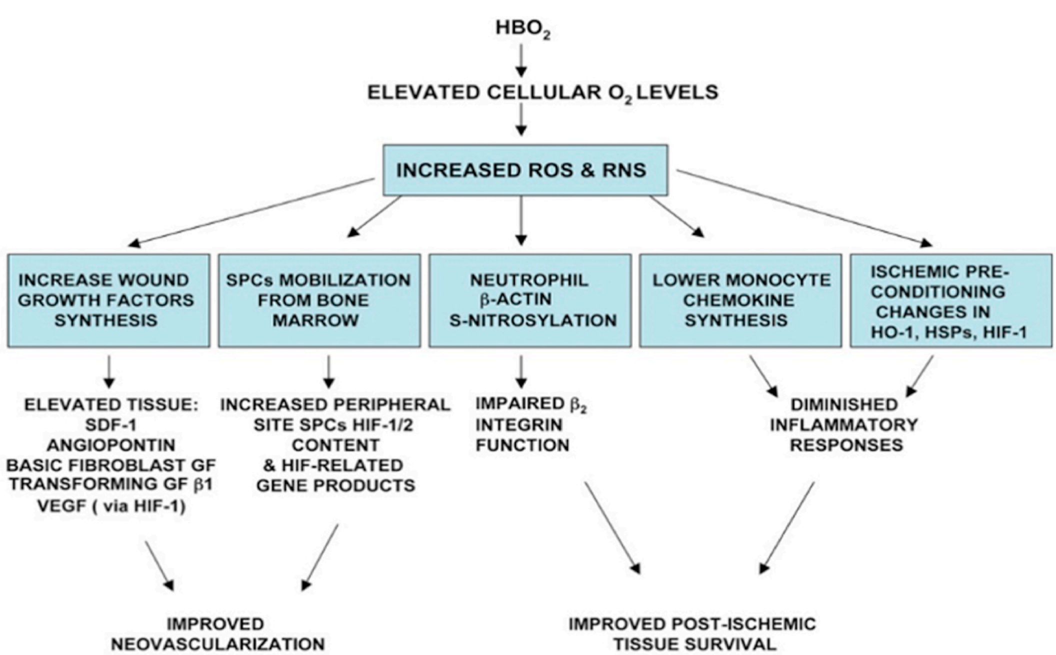

Fig. 1. Overview of the HBOT mechanism associated with increased tissue oxygen pressure. The initial effects (in boxes) resulting from increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and their downstream effectors. Abbreviations: SDF-1 = stromal cell-derived factor 1, GF = growth factor, VEGF = vascular endothelial growth factor, HIF-1 = hypoxia-inducible factor 1, HIF = hypoxia-inducible factor, SPCs = stem/progenitor cells, HO-1 = heme oxygenase-1, HSPs = heat shock proteins [13].

2.2. Data sources & extraction

Data from several HBOT studies centered at the Department of Surgery of Prof. Dr. R. D. Kandou Central General Hospital Manado and Siloam Hospital Manado throughout 2019 and early 2020 were accessed after obtaining the consent of the researchers involved, and the possibility of secondary data analysis was studied. A key consideration is the availability of relevant variables across studies that would allow the data from these studies to be combined for analysis.

The criteria for population, intervention, comparison, and outcome (PICO) were also used in selecting data. Of course, the aspect of the intervention is clear: research for which data were collected to investigate HBOT. The target population was patients who receive HBOT, and in the next selection process, that the patients' diagnoses did not differ too much clinically. The comparison criteria were seen in terms of the outcome. This study assesses the HBOT outcome: successful/satisfactory or failing/unsatisfactory. Then, the groups were compared according to the possible outcome.

Based on these considerations, two HBOT studies that used changes in vascular endothelial growth factor (VEGF) levels as indicators of success were selected. Apart from the relation to VEGF, both studies included the variables of age, sex, leukocyte and platelet counts, and hemoglobin levels in the data collected. These variables were deemed relevant for predicting HBOT outcome and are sufficiently available in the clinical data of most patients, and as such, represent ideal determinants of HBOT choice. No data were missing in the two studies, and only data for patients receiving HBOT were extracted. Of the total 20 and 13 patients, this study identified 10 and 7 HBOT patients from the studies of diabetic foot ulcers and crush injury, respectively. To overcome the small sample size, this study used bootstrap sampling to obtain a sufficient number of observations for analysis. In this case, the data used for analysis has N = 1000 observations.

2.3. Ethical considerations

This study used data previously collected from two studies received ethical approval from the Ethics Commission of Manado Hospital number: 028/EC/KEPK-Kandou/IV/2020. All data were anonymized, and the investigators did not make additional, follow-up contact with the patients. Thus, there were no additional risks to the patients other than those incurred in the primary data collection.

2.4. Data processing and statistical analysis

All data processing and statistical analyses were carried out using statistical software R package version 3.6.3 [22]. The additional packages rpart, ctree, and random forest were the backbone of the decision tree analysis used in this study. Descriptive analyses were carried out by univariate and bivariate methods. The univariate analysis included an assessment of the distribution of each variable, including the normality of numerical variables. This evaluation was carried out using graphs such as histograms, boxplots, and density curves, in addition to the Shapiro-Wilk's normality test. For categorical variables, distribution assessments were performed through frequency tables. The concentration and dispersion values were calculated according to the type of variable and the normality of the distribution for numeric values. For numeric variables with normal distribution, values are given as a mean and standard deviation (SD). For categorical variables, the respective proportion values are displayed. The differences in each variable according to HBOT success status were tested using the *t*-test for numerical variables and the chi-square or Fisher's exact tests for categorical variables.

Decision tree analysis was performed by comparing the results of three methods: classification and regression tree (CART), conditional inference tree, and random forest. The results of the analysis of the first two methods are presented graphically, while the results of the random forest analysis are presented in narrative form, especially regarding the importance value of each predictor variable using the GINI index.

3. Results

3.1. Descriptive statistics

The variables used in the decision tree analysis of HBOT are shown in Table 1, including the original data and bootstrap sampling results. Even though the differences in the number of samples were great, the mean, standard deviation, and proportion of the variables in the bootstrap data were relatively identical to the original data. This is important to guarantee that any analysis of the resulting simulated data can be applied to the population from which the original data were collected. The p-values for the differences in the observed characteristics according to HBOT success status were all significant in the bootstrap data. The large sample size was very decisive in every statistical test, as evidenced in Table 1. In the original data, the differences in age, hemoglobin level, and platelets according to HBOT result status were not supported by the data even though the variables had very small p-values in the test using bootstrap data.

3.2. Analysis using classification tree

The graph of the decision tree analysis using the rpart package in the statistical software R is depicted in Fig. 2. This package applied the CART (classification and regression tree) algorithm. Three variables were used in the 'decision tree' construction, namely leukocyte levels, age, and platelet count. The important values of the variables according to the results of the analysis were levels of leukocytes (34%), platelets (32%), age (26%), and hemoglobin (7%).

Predicting the success of HBOT according to this algorithm began with determining the level of leukocytes: if the patient's leukocytes were ≥14,000 then 24% of HBOT measures will fail. If the leukocyte level was less than that, the next variable that can predict the success or failure of HBOT was age. Ages 67 years or older were more likely to fail in 11% of cases. For younger patients, the determining feature according to this algorithm that will determine the treatment's success is a platelet count

Table 1
Descriptive statistics of research data.

Characteristics (n = 17)	HBOT results			
	Total	Failed	Success	p[a]
Age	48.9 ± 17.4	53.3 ± 18	45.9 ± 17.2	0.407
Sex				
Female	3 (18)	1 (14)	2 (20)	0.001
Male	14 (82)	6 (86)	8 (80)	
Diagnosis				
Crush Injury	7 (41)	3 (43)	4 (40)	0.005
Diabetic ulcer	10 (59)	4 (57)	6 (60)	
Hemoglobin (g/dL)	10.6 ± 1.9	10.7 ± 2	10.5 ± 2	0.868
Leukocyte (x1000)	11.3 ± 4	13.9 ± 4.4	9.4 ± 2.4	0.016
Thrombocyte (x1000)	386.1 ± 163.1	316.9 ± 151.4	434.5 ± 160.3	0.149
Bootstrap data (n = 1000)				
Age	49.5 ± 16.5	53.3 ± 16.3	46.9 ± 16.1	<0.001
Sex				
Female	185 (18)	55 (13)	130 (22)	0.001
Male	815 (82)	356 (87)	459 (78)	
Diagnosis				
Crush Injury	418 (42)	194 (47)	224 (38)	0.005
Diabetic ulcer	582 (58)	217 (53)	365 (62)	
Hemoglobin (g/dL)	10.7 ± 1.9	10.8 ± 1.9	10.6 ± 1.9	0.030
Leukocyte (x1000)	11.4 ± 4	14.2 ± 4.1	9.4 ± 2.3	<0.001
Thrombocyte (x1000)	381.3 ± 161.6	304.8 ± 141	434.8 ± 153.4	<0.001

NOTES: SD = standard deviation, HBOT; = hyperbaric oxygen therapy. [a] *t*-test for numerical variables, χ^2 or Fisher's Exact test for categorical variables.

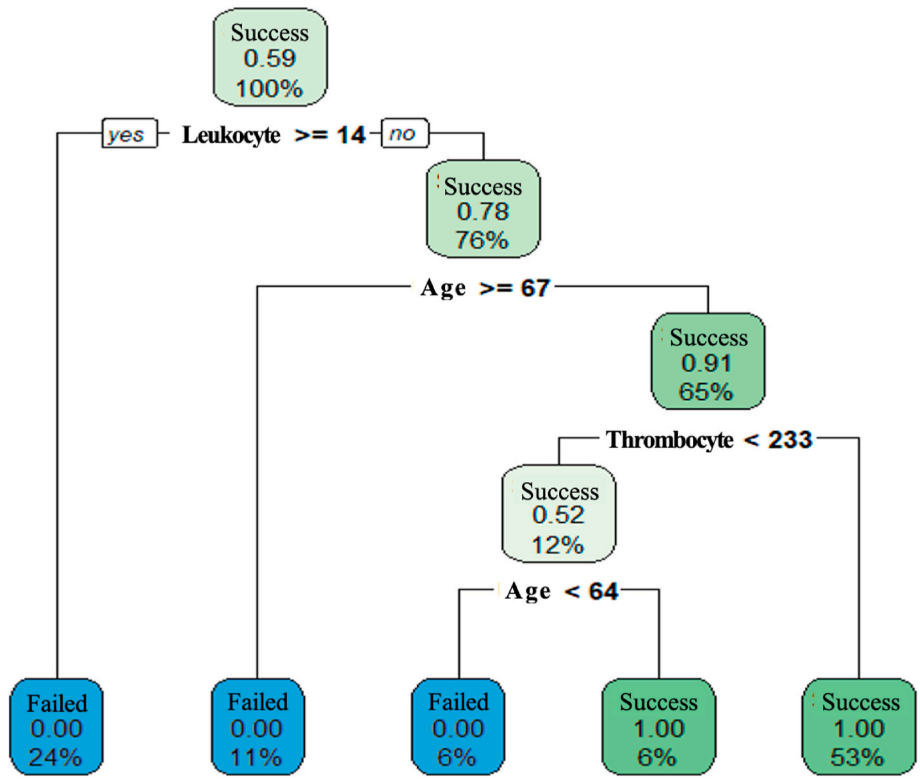

Fig. 2. Result of the decision tree analysis using classification tree.

of at least 233,000. If the patient's platelet count is 233,000 or more, then the success of HBOT can be proven in 53% of cases. Conversely, those with lower platelet amounts still had a 6% chance of benefiting from HBOT if they were between 64 and 67 years of age.

3.3. Analysis using conditional inference tree

The results of the analysis using the conditional inference tree from the Ctree package in R generated results that were broadly similar to the classification tree (Fig. 3). What mainly distinguished the two was the cut-off values for the variables proposed. For example, the conditional inference tree method obtained a leukocyte value of 13,000 as a predictor of HBOT success, 1000 less than identified by using the classification tree. However, interpreting the results of the analysis using the two methods was almost the same.

3.4. Analysis using random forest

The algorithm used by the random forest method for decision tree construction involves 500 trees created through random sampling of the

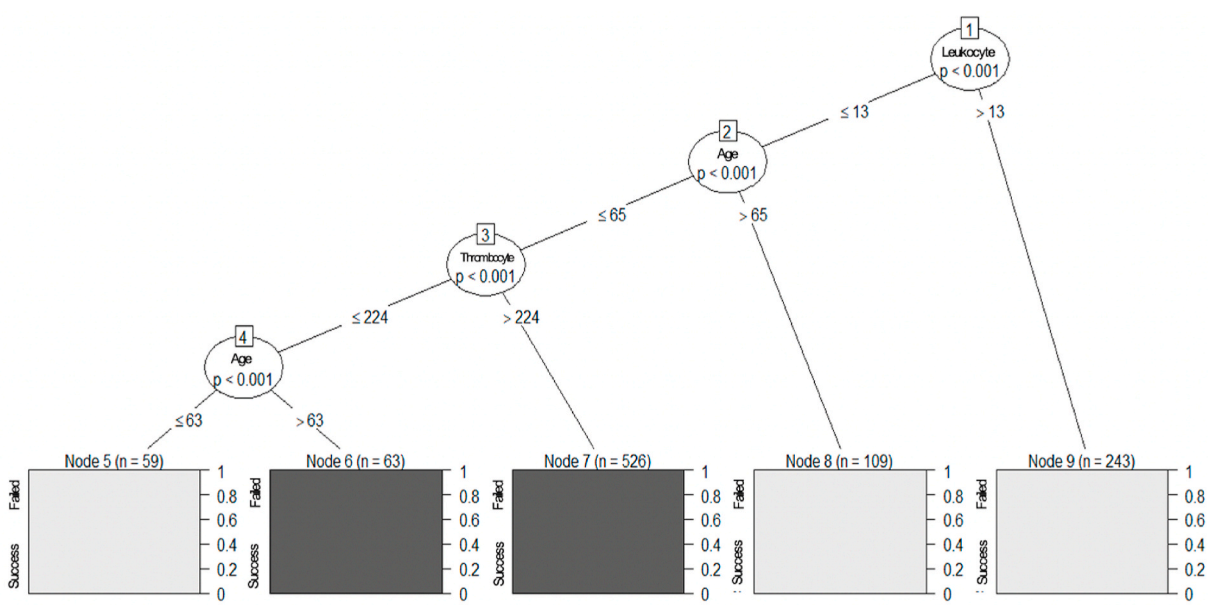

Fig. 3. Results of the decision tree analysis using a conditional inference tree. The light color indicates HBOT failure while the dark box indicates success.

data with a test involving two variables at each split. Due to the large number of "trees", the results of this analysis method can only be conveyed in terms of value. Using the mean Gini reduction (i.e., the index used for the classification tree) as a measure, the random forest algorithm resulted in a sequence of variables according to the level of importance as follows: leucocytes (mean Gini reduction = 207.3), platelets (110.2), age (97.9), hemoglobin (57.9), diagnosis (7.7), and sex (4.3). Mean decrease Gini: Age 92.929891; sex 4.257544; diagnosis 7.725812; hemoglobin 57.910856; leukocytes 207.250536; platelets 110.200315.

4. Discussion

The results of this study indicate that the success of HBOT is determined by several important components, including age, leukocytes level, platelet count, and blood hemoglobin level. Important values for these variables have been discussed based on the classification tree analysis, conditional inference tree analysis, and random forest analysis. The results of the descriptive data in Table 1 showed significant values for age, leukocyte level, and platelet count ($p < 0.001$); while the sex group, diagnosis, and hemoglobin levels were found to be non-significant. Based on the classification tree analysis, the predictors of the success of HBOT were leukocyte level (34%), platelet count (32%), and age (26%). The prediction of the success of HBOT using the conditional inference tree analysis obtained significant levels of leukocytes, age, and platelet counts ($p < 0.001$). These results were similar to the classification tree analysis method. The results obtained from the random forest analysis concluded that the mean value of Gini reduction, leukocytes (207.3), platelets (110.2), age (97.9), and hemoglobin (57.9) can be used as predictors of HBOT success. From these three methods, age, leukocyte level, and platelet count were determinants of successful HBOT; whereas, hemoglobin levels were only significant in one analysis method.

Applying these results in a clinical setting will support the effective use of HBOT as an adjunctive treatment option for patients. Previous studies have proven the efficacy of HBOT in clinical applications for wound healing and reducing inflammation, as indicated by the levels of relevant biomarkers [23,24]. An algorithm to conclude the results from this study is presented in Figs. 2 and 3, where the two decision tree lines taken from the CART and conditional inference tree analyses have similar interpretations.

Based on the existing literature, administering HBOT to patients can reduce blood leukocyte levels [25]. The positive effects of HBOT on blood components and among certain age groups have been discussed in several studies [25,26]. From the results of the present study, a final algorithm is drawn as follows (Fig. 4):

From the results of this study, successful HBOT cannot be separated from determining variables such as age, blood leukocyte levels, and platelet counts. The strengths of this study include simple data collection in which the variable data included laboratory results and demographics, and also the use of predictive methods and analysis models to produce an algorithmic result. On the other hand, the weaknesses of this study are its relatively small sample size (n = 17) and the variety of variables that were extracted. Further research is needed with a larger sample size to identify other groups of variables that can serve as predictive factors for the outcome of HBOT.

5. Conclusions

This study proposed a new algorithm to determine the success of HBOT in a clinical setting based on significant contributing factors such as age, leukocyte levels, and platelet counts.

Ethical approval

All procedure for human experiment has been approved by Ethics Commission of Kandou Hospital Manado, Number: 028/EC/KEPK-Kandou/IV/2020.

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Author contribution

MHO, FLF, EFS and DMA: Design, editing and writing of the manuscript. MCO, FLF, BJK, and HFL: supervision of the paper, and approved the final manuscript. YAL, ANT, and MF: Editing, final review and approved the final manuscript.

Consent

The policy review was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

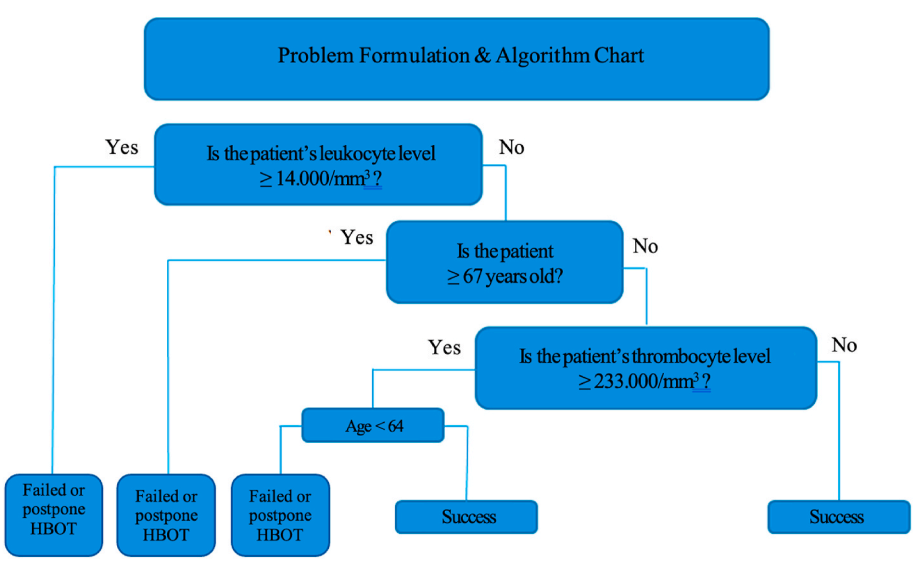

Fig. 4. The algorithm for determining HBOT success in clinical applications.

Registration of research studies

Not applicable as this is a policy review.

Guarantor

Mendy Hatibie Oley.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no conflict of interests.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102725.

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