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Multi-Criteria Model for Evaluating Drugs to Prevent Deep Venous Thrombosis Associated With Orthopedic Surgery: A Hospital-Based Case Study

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ABSTRACT

Background: It's estimated that 40% to 60% of patients undergoing major orthopedic surgery of the hip or knee who do not receive thromboprophylaxis will develop deep venous thrombosis Instituto Nacional de Traumatologia e Ortopedia has established a guideline to prevent DVT with the administration of the Enoxaparin. Recently, institute stakeholders have been questioning this guideline as new oral anticoagulants that offer more comfort and efficacy, but present higher risk of bleeding, have been appearing in the market for treating deep venous thrombosis.

Objective: This study aims to validate the application of a multicriteria decision analysis in a real-world problem, the use of rivaroxaban and enoxaparin to prevent deep venous thrombosis.

Methods: The multicriteria method MACBETH (Measuring Attractiveness by a Categorical Based Evaluation Technique) was used in a decision conferencing process to develop an evaluation model for measuring the relative value of the drugs on each evaluation criterion, separately and globally. The model-building process was informed by a literature review and meta-analysis of randomized clinical trials with a critical appraisal of the evidence.

Results: We report a model-structure with eight criteria, each one associated with a weighting coefficient and value function. Following a simple additive aggregation process, the model-outputs showed that Rivaroxaban was considered a robust option for DVT. Sensitivity analysis and robustness analysis were performed and testify the consistency of the results.

Conclusion: This article contributes to literature by showing how MACBETH method can be combined with scientific evidence and participatory group processes, for health technology assessment in hospitals.

Keywords: anticoagulation therapy, decision support techniques, health technology assessment, MACBETH, multicriteria decision analysis.

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Introduction

The Instituto Nacional de Traumato Ortopedia (INTO) is a high-complexity hospital and a referential center for the Brazilian Ministry of Health's orthopedic surgeries. INTO has recently constituted a Health Technology Assessment (HTA) Nuclei, which supports management decisions. Recently, INTO faced the problem of deciding which drug to adopt for deep venous thrombosis (DVT) prevention in orthopedic surgeries.

DVT is an obstruction of the deep veins due to the formation of thrombi in their interiors and is the leading cause of preventable death in hospitals.[1-3] DVT generally occurs in the lower limbs[1] and can be classified as either proximal or distal. The proximal type includes DVT of the iliac vein, the femoral vein, or located above the popliteal region; this type of DVT is symptomatic. Distal DVT is generally asymptomatic and lies below the popliteal vein, confined to the calf. Estimates indicate that the rates of distal DVT among patients undergoing major orthopedic surgery without thromboprophylaxis vary from 40% to 60%.[2-5] Factors related to the surgical technique and the postoperative period increase the risk of DVT in this setting, increasing the likelihood of complications such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension; prolonging hospitalization time, which has financial consequences on the patient and the health system; and the risk of progression to fatal pulmonary embolism.[2-4,6]

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The use of anticoagulant drugs to prevent DVT is recommended and widely disseminated. These drugs reduce the risk of hospitalized patients with reduced mobility. For many years, warfarin, unfractionated heparin, and low-molecular-weight heparin have been recommended by guidelines[3] as standard prophylaxis that should ideally be established during hospitalization, before or after major surgeries. New oral drugs, particularly rivaroxaban,[2-4,7] have been appearing on the market as alternative drugs to low-molecular-weight heparin because they offer more comfort and efficacy, even if they present a higher risk of bleeding.

Within this context, and given the multiple benefits and risks of these drugs, INTO has realized the need to develop a health technology assessment (HTA) process that could help them in deciding which drug to adopt for DVT. They need support, if they should adopt an injectable drug with more significant experience and safety in clinical practice (low-molecular-weight heparin) or an orally administered drug with limited use (so far) at the institution (rivaroxaban).

The traditional HTA process has been based on incremental cost-effectiveness ratios, where usually exceeding costs of the new technology are divided by the gained quality-adjusted life-years.[8] Recently, the use of incremental cost-effectiveness ratios for HTA has been criticized because it cannot capture all the value (benefits) of the new technologies and other concerns such as equity, decision makers' preferences, and acceptability.[8-11]

Therefore, because of the inadequacy of economic evaluation methods for HTA, the application of multicriteria decision analysis (MCDA) has been growing in recent years. MCDA offers the means to consider a more comprehensive set of benefits compared with conventional HTA methods while still summarizing these benefits in a single number[12] and managing subjectivity transparently. MCDA can improve the quality of healthcare decisions, which "are complex and involve confronting trade-offs between multiple, often conflicting objectives,"[12,13]

Hence, this article aims to build a multicriteria evaluation model according to a hospital-based perspective, without the involvement of the government, insurers, or patients to provide support in deciding which medication should be adopted for the treatment of DVT.[13] Among the relevant aspects in choosing the MACBETH method (Measuring Attractiveness by a Category-Based Evaluation Technique), it is possible to mention the fact that its approach requires only qualitative judgments for presenting a solid theoretical basis and applications in the real world and HTA. Also, the method has several successful experiences in Brazil in different application fields.[13-15] The difference of MACBETH from other methods of multicriteria analysis consists in weighting the criteria and evaluating the options based only on qualitative judgments about differences in attractiveness or value.[13,15] Another advantage is the possibility of build value functions for each criterion.

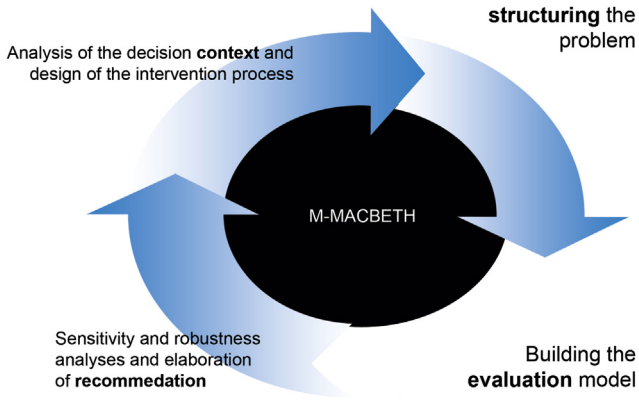
Method

MACBETH

The construction of a MACBETH model involves the development of the following general steps: (1) analysis of the context and structuring of the decision-support process (ie, selection and definition of the criteria); (2) structuring of evaluation elements (ie, measurement of anticoagulant performance); (3) scoring of the options; (4) weighting of the criteria; (5) aggregation of the measured results; and (6) sensitivity and robustness analyses (see Fig. 1).[13]

This method is supported by a computer program, M-MACBETH[16] (www.m-macbeth.com), which was used to build the model and help the decision makers reach their conclusions. The functions of the software were explored to generate both matrices of judgments and value functions as well as scoring and weighing scales for the criteria in which the global attractiveness of each option as well as sensitivity and robustness analyses were obtained to explore the results of the model.[15,16] According to the MACBETH method, rivaroxaban and enoxaparin were evaluated based on qualitative judgments regarding their differences in attractiveness or value across multiple criteria. The name MACBETH is derived from the use of semantic categories regarding the difference in attractiveness (ie, Measuring Attractiveness by a Category-Based Evaluation Technique). Differences in attractiveness among the drugs were evaluated based on the 7 existing MACBETH categories classified as null, very weak, weak, moderate, strong, very strong, or extreme. The options were evaluated indirectly.[12,15,16]

Figure 1. Phases of the MACBETH decision-aiding process.



MACBETH indicates Measuring Attractiveness by a Categorical Based Evaluation Technique.

Sources of Information and Search Strategy

First, a literature review was performed through a structured search with a filter for systematic reviews using the database Medline (via PubMed) up to March 2017. Ten systematic reviews were selected (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2020.08.002). The reviews used composite outcomes (ie, proximal DVT, distal DVT, pulmonary embolism, and death). To build the model, it was necessary to extract the data from primary studies (randomized clinical trials). The quality of the evidence was assessed based on assessing the methodological quality of systematic reviews (AMSTAR) and Cochrane's risk of bias (clinical trials). A search strategy was conducted on the government procurement website to survey the purchase values of rivaroxaban and enoxaparin by INTO. The value does not include intervention, delivery, or training.

Participant Selection

A sample of professionals responsible for the decision-making process at the hospital was selected as participants, ensuring that various perspectives were represented. The following individuals participated: the general director, the pharmacy head, the coordinator of the specialized hip-care center, the coordinator of the specialized knee care center, the coordinator of the specialized trauma care center, a quality-assurance physician, the coordinator of the intensive care unit, and a nurse. Patients were not included.

Criteria Selection

Initially, a list of criteria was drawn up based on the literature review and the opinions of the experts. The criteria selected included the following principles: relevance to decision making, ease of comprehension and measurement, completeness, coherence, nonredundancy, operability, the balance between conciseness/simplicity and completeness/complexity, and preferential independence.[12,17,18] The final criteria list was submitted to validation by the decision makers and presented in Table 1.

Decision Conference

Support for decision making using the MACBETH method incorporates the constructivist approach to decision making, that is, strategic meetings that enable interactions among participants and mutual learning to create a deeper understanding of the problem based on the assessment of multiple dimensions.[12,17,18]

The decision conference was held at INTO with 8 decision makers (ie, professionals with vast experience directly involved in the management of the institution) who came to conclusions. The preferences were shared and debated among participants to reach group consensus. They were supported with the assistance of a trained analyst and facilitator to ensure the neutrality of the information and impartiality throughout the process. The meeting occurred in a large, suitably equipped room with chairs arranged in a U-shape to ensure the complete visualization of the information projected by the computer on the screen to create a productive environment for the group in which to work.[12,17,19]

Sensitivity and Robustness Analysis: Model Validation

A sensitivity analysis was performed for each criterion weight to analyze the extent to which the model's recommendation would change as a result of changing the weight on one criterion at a time.[13] Further, a robustness analysis to investigate what were the model's results in light of uncertainty and incomplete preferential information was also performed. The following parameters were changed: the cardinal information (referring to the scales); MACBETH global information (referring to judgments); removing the criterion "total cost of treatment." "Thrombocytopenia" was selected to insert imprecision due to low-quality evidence.

Results

Value Tree and Options Performance

Figure 2 depicts the criteria structured in a tree form that were defined in the decision conferencing. The description of each criterion and the respective descriptor is depicted in Table 1.

The performance of the options within each criterion was obtained via meta-analyses (see Supplemental Materials found at https://doi.org/10.1016/j.vhri.2020.08.002) of the selected randomized clinical trials that worked with a primary composite outcome including distal DVT, proximal DVT, nonfatal pulmonary embolism, and all-cause death[20-25] (see Table 2). The absolute risk and reliable estimates[12] of each alternative for each criterion were extracted, and the results were presented in absolute values for every 1000 patients during the postoperative period to facilitate their interpretation.

Scoring and Weighting

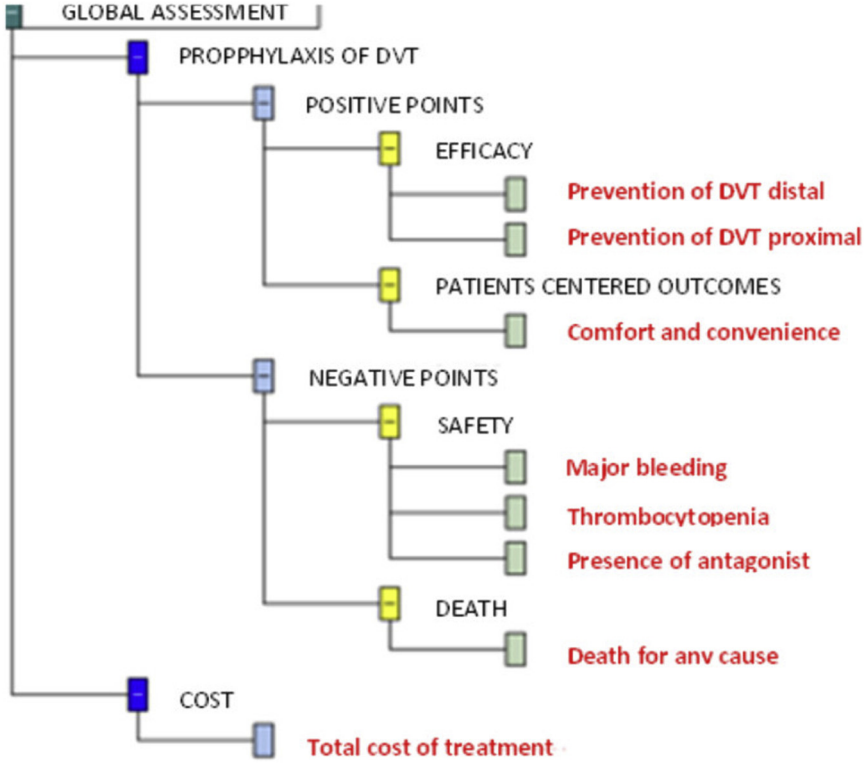
The score of each drug on each criterion (see Table 3) was assessed by applying a value function that enables converting the drug's performance into a value score. Value functions were built to convert performance levels into scores, that is, value functions reflect the preferences of decision makers for different levels of performance on a measurable scale.[12,18] Relative weights for each criterion were also determined that enable the harmonization of those partial scores and their synthesis in overall value. The weights show that the most important criteria were death from any cause, major bleeding, and proximal DVT prevention. For decision makers, preference to avoid "death for any cause" is the most essential criterion in the model, where all efforts must be concentrated to achieve that goal.

Table 1. List of criteria and respective descriptors.

Dimensions	Criteria	Description of the criteria	Descriptor
Efficacy	Prevention of DVT distal Prevention of DVT proximal	Asymptomatic DVT detected by venography Symptomatic DVT	Number of cases per 1000 patients during the postoperative period Number of cases per 1000 patients during the postoperative period
Patient-centered outcomes	Comfort and convenience	Administration route	Oral and subcutaneous
Safety	Major bleeding Thrombocytopenia Presence of antagonist	Bleeding was fatal, that involved a critical organ, or that required reoperation or clinically overt bleeding outside the surgical site that was associated with a decrease in the hemoglobin level of 2 g or more per deciliter or requiring infusion of 2 or more units of blood. Reduction by at least 50% of platelet count. Presence of antagonist for blocking the anticoagulant action of drugs.	Number of cases per 1000 patients during the postoperative period Number of cases per 1000 patients during the postoperative period No specific reverser Partial reverser
Death	Death for any cause	Deaths that occurred during the treatment period.	Number of cases per 1000 patients during the postoperative period
Cost	Total cost of treatment	Total cost of the drug for the prophylaxis of DVT in hip arthroplasty considering 28 days of treatment.	Total cost of prophylaxis after hip arthroplasty

DVT indicates deep venous thrombosis.

Figure 2. Measuring Attractiveness by a Categorical Based Evaluation Technique tree to evaluate DVT prophylaxis during the period after major orthopaedic surgery.



DVT indicates deep venous thrombosis.

Table 2. Option's performance.

Options	DVTP	DVT-D	Comfort	Bleeding	Death	Reverser	Cost*	Thrombocytopenia
BANA	5.6	36	VO	4.2	1.8	No reverser	160.44	0
PARINA	25	68	SC	2.7	3.3	Reverser partial	308.00	2

BAN indicates rivaroxaban; DVT, deep venous thrombosis; DVT-D, deep venous thrombosis distal; PARIN, enoxaparin.
*Total drug cost in reais for DVT prophylaxis in total hip replacement considering 28 days of treatment.

Table 3. Criteria weighting (global assessment).

	[Death]	[Bleeding]	[DVT P]	[DVT D]	[Antagonist]	[Trombocit]	[Cost]	[Comfort]	[No ideal]	Current scale	Extreme
[Death]	No	Strong	V.Strong	Extreme	Extreme	Extreme	Extreme	Extreme	Extreme	28.66	Very Strong
[Bleeding]		No	Moderate	Positive	Positive	Positive	Positive	Positive	Extreme	19.11	Strong
[DVT P]			No	Strong	Positive	Positive	Positive	Positive	V.Strong	15.92	Moderate
[DVT D]				No	Moderate	Positive	Positive	Positive	Strong	12.10	Weak
[Antagonist]					No	Weak	Strong	Strong	Strong	8.92	Very Weak
[Trombocit]						No	Weak	Weak	Strong	6.37	No
[Cost]							No	Weak	Strong	5.10	
[Comfort]								No	Strong	3.82	
[No ideal]									No	0.00	

BAN indicates rivaroxaban; DVT-D, deep venous thrombosis distal; DVD-P, deep venous thrombosis proximal; PARIN, enoxaparin.

Table 4. Table of scores.

Options	Overall	DVT D	DVT P	Comfort	Bleeding	Trombocit	Antagonist	Death	Cost
BAN	71.82	80.00	96.31	100.00	30.00	100.00	0.00	90.00	99.73
PARIN	45.55	4.44	0.00	0.00	55.00	75.00	100.00	71.25	7.50
[tudo sup]	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
[No ideal]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Weights:		0.1210	0.1592	0.0382	0.1911	0.0637	0,0892	0.2866	0,0510

BAN indicates rivaroxaban; DVT-D, deep venous thrombosis distal; DVD-P, deep venous thrombosis proximal; PARIN, enoxaparin.

Global Score

The overall drug scores were obtained through a simple weighted sum process. According to the criteria considered and based on the judgments made, the results of the model showed that rivaroxaban (BAN) was the option with the highest global score (71.82 points) compared to enoxaparin (PARIN; 45.55 points); see Table 4. To explore the differences in value between the 2 drugs, it was possible to verify that the performance of rivaroxaban in the comfort criteria, and the proximal DVT, was outstanding in the composition of its overall value. Comfort and lower incidence of proximal DVT are gained and lost with increased risk of bleeding and the absence of reverser.

Model Validation: Sensitivity and Robustness Analysis

All the criteria were analyzed, and the model's recommendations changed in only 2 cases: if the weight on major bleeding changed from 19% to greater than 60.4% or if the weight on the absence of antagonist increased from 9% to greater than 27.8%.[26] Both situations were considered by the authors to be implausible.

Even with the restrictions imposed on the model in the robustness analysis, all of this process demonstrated that it was robust to conclude that rivaroxaban is globally more attractive than enoxaparin.

Discussion

This work has an important local potential impact, since were built with HTA professionals, physicians, nurses, pharmacists, and hospital managers. Hospital-based HTA is a new area with limited evidence and methods.

The decision regarding DVT prophylaxis after major orthopedic surgery (ie, injectable vs oral drugs) is made based on the trade-off between the comfort of the oral drug, the reduction of the risk of thrombosis, and the increased risk of bleeding.

The clinical trials that supported the model used composite outcomes that are attractive for those conducting the study because they require small number of participants; however, the interpretation of the results might be misleading in that they overestimate the effect of interventions. A composite outcome assumes that the treatment effect is homogeneous for all results included.

By performing a critical analysis of the evidence, methodological limitations were observed, such as the use of a modified intention-to-treat analysis, a strategy that reduces confidence in the evidence and impairs randomization. Despite this limitation, the level of evidence was acceptable, showing that rivaroxaban is at least similarly efficacious, if not more effective, than enoxaparin.

One of the limitations of this study is that it did not include patients in the decision conference. The authors considered that a specialized training for patients about HTA concepts would be necessary. Another observed difficulty is the limited knowledge of epidemiology by the decision makers. About the information to feed the model, there was limited evidence for patient-reported outcomes.

In orthopedic hospitals, enoxaparin is also widely prescribed for prevention; therefore, the current model's results are contrary to the institution's practice. Some factors should be analyzed to explain this predilection, such as experience in treatment management, the reduced risk of thrombocytopenia compared to unfractionated heparin, well-established use in clinical practice, and aversion to the risk of bleeding based on oral anticoagulant use.

Regarding the sensitivity and robustness analyses, we observed that for the model recommendation to be changed, substantial and likely unfeasible changes in weights would be necessary, indicating the robustness of this model.

Representing the problem in the form of a value tree organized by the criteria enabled us to broaden its general view, thereby preventing decision making from occurring intuitively and encouraging the contemplation of several dimensions simultaneously in a structured way to facilitate the understanding of the problem.[12,18,27]

Recently, HTA studies have increasingly indicated the need to adapt conventional approaches using a multiple criteria assessment approach because of the different characteristics of patient populations and technologies, especially in situations where the use of cost-effectiveness analysis is questioned. Specifically, when assessments are based only on this analysis, uncertainty exists regarding the benefits, and these analyses favor only low-cost therapies that jeopardize innovations and disregard nonmonetary values such as the inclusion of vulnerable groups and the prioritization of children. Multicriteria analysis has been used for decisions in which it is necessary to identify priorities in the incorporation of technologies, including the trade-off between advantages and risks of the evaluated technologies, in financing, investment, reimbursement, regulation decisions and in the decision shared between patients and doctors regarding the evaluation and selection of therapies.[19,26,28]

In examining decision makers' participation, we observed that one of the participants gained a better understanding of the method and was conspicuous throughout the discussion. This participant's confident performance with well-founded considerations at each judgment contributed to the sharing of visions, experiences, and perspectives within the group.[12,28] At this type of meeting, it is possible to have a "herd effect" wherein a participant or group of participants polarize the discussion based on convictions sustained by a type of conflict of interest; however, this case was not observed in the current study.

The technique used to obtain weights is called "swing weights" and ensures that decision makers will analyze the criteria based on the scale of benefits and the references to avoiding the so-called most common critical error.[29] The understanding of this technique among the decision makers was considered the most challenging part of this study.

Also, regarding the limitations and challenges inherent to all methods and present in this study, we emphasize that the indirect scoring process of MACBETH incorporates a certain degree of subjectivity, especially during the criteria weighting stage, which requires more considerable assistance to be conducted. The decision makers had difficulty understanding the judgments requested, and it is essential to consider the cognitive capacity of the participants or the number of judgments required in the matrix because these variables can make the process wearying and complex. The need for at least 2 people, an analyst and a facilitator, to apply the method is a disadvantage of its use.

Another point to emphasize is that the interpretation of higher scores still lacks discussion and study. A drug with higher scores will not automatically be incorporated into patient care. How MCDA techniques and scoring advantages influence decision making in an HTA should be discussed. Clearly, the method favors an in-depth understanding of the problem and more informed decisions; on the other hand, it can influence the incorporation of technologies that are not cost-effective.

Ideally, a decision conference should include the participation of patients to capture their preferences; however, this result was not feasible given deadlines and the absence of patients with previous training needed to understand concepts such as risk and quality of evidence.

In turn, we highlight as favorable aspects such as the performance of qualitative judgments in a model structured by indirect comparisons that are generic, with the possibility of other drug comparisons using the same objective (eg, with new drugs to prevent DVT).

In light of the above, it remains essential to reinforce that both MACBETH and any other MCDA approaches do not replace the role of qualified decision makers; instead, these techniques should assist them in finding the solution that best fits their judgments, needs, and preferences.

It is essential that the method also be applied to other complex public health decisions so that the method shows practical improvement and adaptation concerning the HTA setting and the guidelines consolidating the best practices for their use in the context of the health management.

The performance of this study was a positive and innovative experience. Each step was conducted systematically, allowing the problem to be structured transparently and consistently. It is crucial to highlight the subjective character of the evaluations and assignment of weights carried out, inherent in every decision-making process.

Conclusions

The decision-making process is full of subjectivity; this study took a constructivist approach whose assessment was based on decision makers' value judgments, priorities, and preferences and the needs of the setting to integrate the process systematically and transparently.

The performance of rivaroxaban and enoxaparin was supported by scientific evidence in association with consensual deliberations obtained through judgments of attractiveness differences during the decision-making process. The results of the model indicate that rivaroxaban was the most important anticoagulant according to the decision makers' preferences, with 71.62 points. The results suggest that it was the most appropriate option in the study scenario. The method helped decision makers by leading them to a defensible choice of the most valuable anticoagulant for the institution according to their preferences. The model's results help decision makers achieve the best decision, while also allowing these results to be explored in different contexts. Our results present the possibility of applying a comparative analysis of technologies based on multiple criteria in a hospital setting.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2020.08.002.

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