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Integrated environmental and health economic assessments of novel xeno-keratografts addressing a growing public health crisis

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Tissue scarcity poses global challenges for corneal transplantation and public health. Xeno-keratoplasty using animal-derived tissues offers a potential solution, but its environmental and economic implications remain unclear. This study evaluated two xeno-keratoplasty procedures at a single institution: (1) native corneas (Option 1) and (2) tissue-engineered corneal scaffolds derived from slaughterhouse waste (Option 2). Life cycle assessment (LCA) quantified environmental impacts across 18 midpoint indicators, while cost-effectiveness analysis (CEA) incorporated cost and environmental impact using two approaches. Option 1 exhibited significantly lower environmental impact than Option 2 across most indicators, primarily due to the energy and equipment demands of cell culture in Option 2. Both CEA approaches (carbon offset pricing and utility decrement) demonstrated cost-effectiveness dominance for Option 1. Xeno-keratoplasty using native corneas (Option 1) appears more environmentally and economically favorable than tissue-engineered scaffolds (Option 2) in the current analysis. Future studies could explore diverse xeno-keratoplasty techniques for optimizing sustainability.

Keywords Xeno-keratoplasty, Corneal transplantation, Environmental impact, Cost-effectiveness analysis, Slaughterhouse waste, Circular economy

The healthcare sector is a significant driver of both economic growth and environmental emissions in the United Arab Emirates (UAE). According to reports from the Ministry of Economy in the UAE, overall spending on healthcare in this nation is anticipated to increase from US $21 billion to US $26 billion between 2021 and 2026[1]. Currently, the overall expenditure on healthcare in the UAE stands at approximately 4% of its GDP, which is greater than the average for OECD countries. Coupled with this economic growth is the increase in environmental impacts of healthcare, with overall greenhouse gas (GHG) emissions exceeding 20 million tons CO_2-eq per capita since 2020[2]. This current vision of the UAE government aims for a reduction in environmental emissions without jeopardizing economic growth.

The healthcare sector offers the opportunity to meet this objective by reducing resource consumption through waste minimization. Additional emission reduction can be achieved through efficiency improvements in the procurement supply chains. This approach, in turn, requires a rethink of the current practices to create room for novel solutions and innovation in biotechnology and the life sciences. This study also focuses on a novel solution, i.e., xeno-keratoplasty derived from slaughterhouse waste, which promises to remedy the public health burden of corneal diseases in a manner that is both economically and environmentally sustainable.

Recent advancements in regenerative medicine are propelling the emergence of xeno-keratoplasty as a promising alternative to traditional corneal transplantation[3–5]. Traditional keratoplasty, which often relies on human cadaveric donors, involves the partial or complete replacement of corneal tissues based on injury severity and location[6]. This procedure aims to restore vision, alleviate pain, and enhance the appearance of damaged or diseased corneas. However, challenges, such as the high incidence of end-stage corneal blindness[7], scarcity

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of human corneal tissues[8,9], and complications leading to graft rejection[10], are driving the exploration of both synthetic and natural alternatives to address the global need for corneal transplants[11].

One such alternative is xeno-keratoplasty, which focuses on developing grafts from various animal-derived sources, such as monkeys, pigs, rabbits, and sheep. The novelty of this procedure relies on the production of personalized corneal grafts using a substantial and well-documented combination of advances in gene therapy, tissue engineering, and adaptive manufacturing, as well as primary/stem cell allocation, differentiation, and scaffolding techniques[5,12–16]. For instance, Wang et al.[4] recently extended this approach to devise a sustainable keratoplasty model, which utilizes native corneal extraction techniques and surfactant-based decellularization, aiming to produce a virtually limitless supply of corneal xenografts with the aid of advanced computational approaches that examine subtle changes in cell and tissue structure[3,17,18]. This process uses native (innate) abattoir tissues, as well as their tissue-engineered derivatives generated from acellular scaffolds.

Currently, donor corneas derived from animals, such as porcine and bovine sources, have been explored as alternatives due to their structural similarities to human corneas[14]. Porcine corneas, in particular, are widely studied for their availability and size compatibility. These xenografts are typically decellularized to reduce immunogenicity, which removes cellular material while preserving the extracellular matrix (ECM), creating scaffolds for transplantation. However, concerns remain regarding the risk of xenozoonosis and the challenges of maintaining pathogen-free conditions during processing.

Xenografting with the native cornea is considered a viable option due to the remarkable immune-privilege nature of the cornea. This characteristic allows the cornea to tolerate the introduction of antigens without eliciting an inflammatory immune response, thereby reducing the possibility of rejection and enhancing long-term graft survival post-transplantation[14]. In comparison, a large body of scientific literature demonstrates how decellularization/recellularization techniques offer a novel solution to generate personalized grafts for various tissues and organs incorporated with a recipient's cells[19–26]. Specifically, decellularization creates ECM-rich, acellular scaffolds by removing the cellular and genetic components of original tissues that can be used as templates to create viable patient-specific corneal substitutes through the recellularization (reseeding) process using their primary/stem cells.

Existing research on the topic is conspicuous by its absence. Hitherto, no study has been conducted to evaluate the environmental impact of keratoplasty. What's more, there hasn't been any study that evaluates both health technology assessments (HTA) and life cycle assessments (LCA). The present study is unique in modeling both health, economic, and environmental impacts simultaneously. As such, this study can be used as a template for future studies combining HTAs and LCAs.

Accordingly, we have focused on ovine-derived corneal scaffolds collected from slaughterhouse waste. This approach is aligned with the goal of creating a sustainable model for xeno-keratoplasty, repurposing slaughterhouse by-products for clinical use. While porcine models are more commonly discussed, ovine-derived corneal scaffolds provide an additional option that supports sustainability and reduces environmental impact. Our analysis extends beyond the biological feasibility of using these xenografts and incorporates a comprehensive environmental and economic assessment through life cycle analysis (LCA) and cost-effectiveness analysis (CEA). This positions our study within the broader context of xeno-keratoplasty while emphasizing the potential benefits of utilizing ovine corneal scaffolds.

## Materials and methods
Study design
This study used a process-based LCA to quantify the environmental impacts of two distinct xeno-keratoplasty procedures involving native corneas and the decellularized corneal scaffolds that can be regenerated as individualized grafts. These procedures occurred at the Khalifa University's College of Medicine and Health Sciences (KU CMHS) in Abu Dhabi, UAE. This organization is one of the top-ranked institutions involved in regenerative medicine in the UAE, generating hundreds of xenograft models annually, and is involved in primary and stem cell-based tissue engineering to address the substantial and growing need for corneal transplantation. The functional unit for the procedure was a single xeno-keratoprosthesis model involving a single ovine eye.

Xeno-keratoplasty model derived from slaughterhouse waste
All tissues were collected from the Abu Dhabi Automated Slaughterhouse, which is one of the largest slaughterhouses in the UAE, capable of accommodating around 37,000 sacrifices and carcasses. For our purposes, the ovine eyes were collected from the animals directly after slaughter and transported to KU CMHS, where they were used to create xenografts for our in vitro transplantation model, presented in Fig. 1. The model consists of allogeneic native corneas and tissue-engineering personalized xenografts derived from decellularization/recellularization techniques transplanted on extracted eyes obtained from other animals. In-depth details on native and tissue-engineering processes[3,4] and transplantation[27] are outlined in the literature. All experimental protocols were approved by the Animal Research Oversight Committee (AROC) at Khalifa University of Science and Technology. The study was also carried out in compliance with the ARRIVE guidelines. All methods were carried out in accordance with relevant guidelines and regulations.

Corneal processing and xenograft preparation
The protocols for processing both native corneas and tissue-engineered corneal scaffolds used in this study were based on methodologies established in our previous research[3,4,28]. Fresh ovine eyes were sourced from the Abu Dhabi Automated Slaughterhouse and transported to KU CMHS under sterile conditions. In earlier studies, native corneas were excised, washed in sterile saline, and treated with antibiotics to minimize contamination. These corneas were evaluated in their unmodified state, focusing on structural integrity, transparency, and biomechanical properties (reference to the relevant previous study).
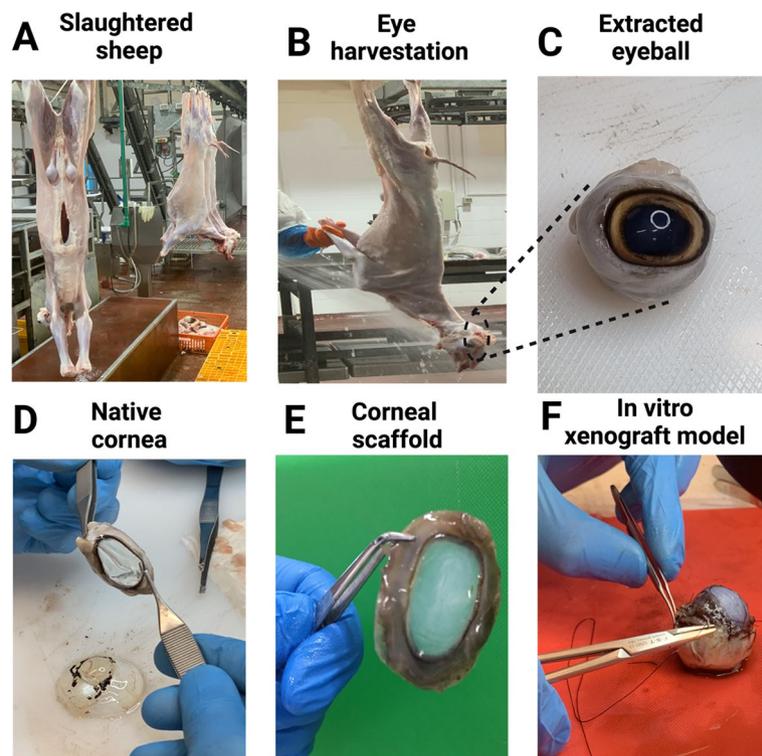
Fig. 1. Corneal xenografts generated from whole waste obtained from the Abu Dhabi Automated Slaughterhouse. (**A**) Images of sheep freshly slaughtered, (**B**) Slaughterhouse worker preparing to extract whole eyes from an animal, (**C**) An extracted eyeball, (**D**) Native cornea excised from the whole eye, (**E**). A corneal scaffold created from decellularization/recellularization technologies, and (**F**). The in vitro xeno-keratoplasty model.

We previously employed a decellularization process for the tissue-engineered corneal scaffolds using a 4% zwitterionic biosurfactant solution, followed by rigorous washing to remove residual surfactants. These decellularized scaffolds were analyzed through histological and polymerase chain reaction (PCR) assays to confirm the absence of cellular materials and pathogens. The outcomes of these assessments provided the groundwork for evaluating the potential of decellularized corneas as xenografts[28].

While the current study did not directly repeat these experiments, we built on these previously validated processes to perform a comparative life cycle analysis (LCA) and cost-effectiveness analysis (CEA) of native versus decellularized corneal scaffolds derived from slaughterhouse waste. This analysis was used to assess the environmental and economic implications of utilizing these materials in clinical settings.

Product life cycle model

The Life Cycle Assessment (LCA) conducted in this study aimed to quantify the environmental impacts of xeno-keratoplasty by following a structured, multi-step approach based on the ISO 14,040 framework. The LCA included the four main stages: goal and scope definition, life cycle inventory (LCI), life cycle impact assessment (LCIA), and interpretation. Below, each parameter used in the LCA is detailed based on how it was determined and evaluated.

Goal and scope definition
The goal of the LCA was to assess the environmental impacts of a single xeno-keratoplasty procedure, from tissue harvesting to post-operative patient care. The functional unit chosen was chosen as the production of one pair of corneas derived from sheep for transplant. The system boundary was set to include all processes from sheep tissue harvesting, sterilization, packaging, and transportation to the operating room procedures and end-of-life scenarios to perform each type of keratoplasty. Exclusions included environmental impacts outside the control of the procedure itself, such as personal transportation of patients to clinics and hospital energy use unrelated to the surgery. Sensitivity analyses were conducted to evaluate the importance of these exclusions. All inputs were attributed by weight and normalized accordingly. As such, impacts associated with the processing and packaging of meat, skin, and other products were not included in this study. The system boundary is shown in Fig. S1 in the Supplementary file. It is important to note that for the subject analysis, only the attributable life of the equipment used will be considered. Assumptions regarding the useful life of the inputs and attributable proportion thereof have been provided in the Appendix. As such, some inputs (e.g., drapes) were not considered in the analysis as their life depends upon the quality of the fabric and involve inputs related to washing, ironing, and repackaging, which are beyond the scope of the current study.

Life cycle inventory (LCI)
The life cycle inventory phase involved collecting quantitative data for each stage of the xeno-keratoplasty process. Each parameter was measured, estimated, or sourced from existing LCA databases such as the Ecoinvent database. Data were gathered on sheep cornea extraction, including energy use, water consumption, and waste generation. Information regarding the sterilization process was obtained from hospital records, including energy use, chemicals involved (e.g., ethylene oxide), and water consumption. The environmental footprint of materials was derived from Ecoinvent. Transportation impacts were calculated based on the distance travelled by the harvested cornea tissue from the animal facility to the surgical center, and by considering the transportation mode (i.e., refrigerated truck). Standard emissions data for transportation were used, including fuel consumption and greenhouse gas emissions per kilometer travelled. Detailed data were collected on the surgical instruments used, including single-use items (gloves, scalpels, sutures) and their disposal. Energy consumption (electricity for lighting, HVAC, and surgical equipment) was estimated using hospital energy audits. Data on waste generation (hazardous and non-hazardous) during surgery were also documented.

Life cycle impact assessment (LCIA)
The LCIA phase translated the inventory data into environmental impacts using an impact assessment model. SimaPro software was used to estimate 18 midpoint indicators using ReCiPe methodology with a Hierarchical perspective. Where data was missing from the Ecoinvent database for individual inputs, published protocols were implemented based on chemical characteristics or functional parallels These parallels were confirmed by the owner of the case study as appropriate to the scope of the study. The equation for the contributions of individual emissions within the system, is given in equation (1).

$$Process\ LCA = \sum\nolimits_{i=1}^{n} A_{p(i)} \times E_{p(i)} \tag{1}$$

Here Ap represents the inputs (i) into the supply chain, according to the system boundary shown in Fig. 1; this includes raw material extraction, energy use, and production processes; n is the total number of inputs (i), and Ep is the emissions intensity of the chosen impact categories outlined above, for each input (i) into the supply chain. A detailed explanation of LCA parameters has been provided in the Supplementary file.

Interpretation
The final phase of the LCA involved interpreting the results to identify the most significant contributors to the environmental impact of xeno-keratoplasty. Sensitivity analysis was conducted to explore how changes in key parameters (e.g., transportation distance, energy use) affected overall results. Recommendations for reducing the environmental impact of xeno-keratoplasty were drawn from this phase, emphasizing areas such as optimizing transportation logistics and improving energy efficiency in sterilization processes.

Results
Life cycle assessment
The results of the LCA are given in Fig. 2 below, which provides the values for fifteen of the 18 midpoint indicators against both options (Table S2). A complete list of the indicators with corresponding values has been provided in the Supplementary file as Table S1. For greater clarity, the impacts from the transplant stage have been shown as distinct from those involving cornea extraction and cell culture development. It is important to mention that the figure below does not include values for end-of-life disposal scenarios. This is because of the lack of complete data regarding the sheep carcass, skin, and other leftovers. It can be seen from Fig. 2 that the impacts from Option 2 (corneal scaffold) were generally higher than those from Option 1 (native cornea). This is mainly due to the inclusion of equipment and energy for cell culture development that would drive patient-specific recellularization.

Figure 3 below shows the midpoint indicators of the sub-components of Options 1, 2, and the transplant stage (Table S3, Table S4, and Table S5). It also shows the combined values after adding the environmental impacts of the transplant stage to each of the two options on a log scale. It can be seen that the largest impacts were driven by the use of disinfecting agents (Ethanol) in all cases. The use of tissue papers in Options 1 and 2 also had relatively high environmental impacts. Inputs such as sharps, plastics, OT table, etc., had relatively lower impacts as their useful life for the purpose of cornea extraction and transplant was considered. This meant that their impacts were lower than those of single-use items such as disinfecting agents, fixatives (formalin), etc.

Similarly, impacts from transportation were quite low due to the very low weight of the cornea attributable to the transport stage. Similarly, electricity use was 2 h in the cornea extraction and 1 h in the transplant stage, and hence, its environmental impacts were not as significant as those from other inputs. The key takeaway from the bar chart displaying log values is that option 2 + transplantation has greater environmental impacts across all categories as compared to those from option 1 + transplantation.

It is important to mention here that the LCA did not account for the use of anesthetics or immunosuppressants owing to the lack of availability of pertinent data in LCA databases. Still, there has been at-least one study assessing the Global Warming Potential (GWP) of anesthetics, which uncovered a wide variation in results between different types[29]. Similarly, there have been a few studies on the GWP of steroids (e.g., for asthma), of which some (corticosteroids) are comparable to immunosuppressants. One study found such steroids to have a GWP of 28 kg CO_2-eq per inhaler[30]. In the present case, the GWP could be larger depending upon the duration of the use of immunosuppressants in the form of eye drops. Post-operative complications would lead to further resource use, thus increasing the environmental burdens even further.
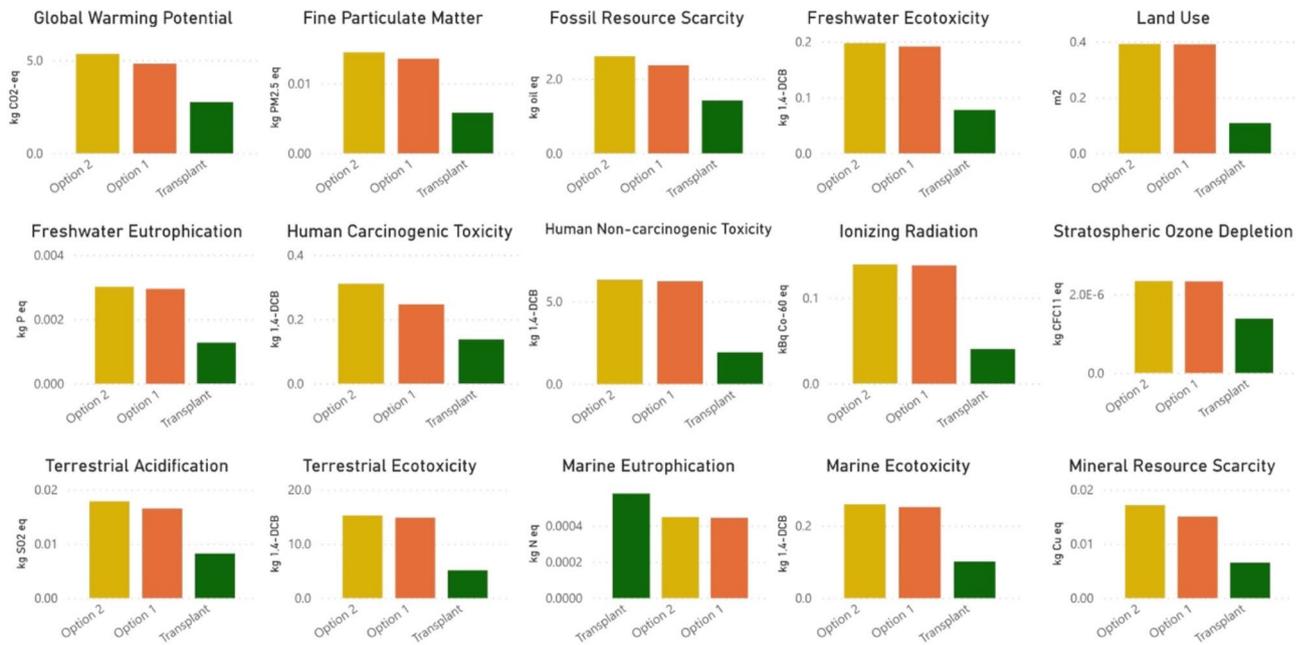
Fig. 2. Life cycle impact assessment from the two options and the transplant stage for 15 midpoint indicators.

Cost-effectiveness analysis

For a cost-effectiveness analysis (CEA), the utilities of the two options were taken from the literature, and the costs were obtained from the hospital records. For an integrated impact assessment, we used two approaches. In the first approach, the environmental costs were added to the individual costs of the two options. In the second option, the utility decrement from the environmental impact was incorporated into the individual utilities. For the first approach, the cost of environmental impacts was estimated using the cost of carbon offsets as reported at the innovative carbon exchange maintained by Abu Dhabi-based air-carbon exchange[31]. For the second approach, the DALYs were used from the end-point impact categories of the two options and converted into QALYs using the conventional conversion rate (QALY gained = 1.228 x DALY saved).

The Incremental Cost Effectiveness Ratios (ICERs) for both approaches have been given along with the utilities and the costs, as shown in Table 1. It can be seen that Option 1 was dominant. The chosen Willingness to pay (WTP) threshold corresponds to the GDP per capita of the UAE (AED 1,81,613.00) and was chosen due to the absence of any existing threshold. The probabilities used in the calculations have been provided in the Supplementary file. It is important to mention here that while the decision tree model (Figure S3) accounts for minor/major complications after the keratoplasty, the LCA in this study is limited to the transplant stage. Similarly, while the cost-effectiveness assessment takes into account the costs of drugs, the LCA does not include their environmental impacts. This is one of the limitations of this study, which can be addressed if pertinent details can be obtained from drug manufacturers or pharmaceutical companies.

It can be seen that the results were identical for both approaches. This is because of the cost of carbon (AED 0.3/kg CO_2-eq), as well as the very low endpoint health impacts as measure by LCA, i.e., 1.95E-05 DALY and 2.00E-05 DALY, respectively. This shows that even if the emissions increase 1000-fold, the overall results presented in Table 1 will not change much. Thus, the exclusion of drugs from the LCA doesn't seem to have created a huge difference. This also shows one of the challenges of incorporating environmental costs and benefits in the traditional CEAs.

Figure 4 below displays, graphically, the distribution of emissions against costs and QALYs for both options. It shows that the GWP per unit cost (GWP/AED) was 4.03E-04 kg CO_2-eq/AED and 3.80E-04 kg CO_2-eq/AED, respectively for options 1 and respectively. Thus, while the overall costs and emissions were higher for option 2 in absolute terms, their ratio seems to favor option 2 as a more sustainable option. On the other hand, the GWP/QALY was 1.89E + 02 kg CO_2-eq and 2.94E + 02 kg CO_2-eq for options 1 and 2 respectively. In this case, option 1 is relatively better than option 2 in both absolute and relative terms.

Discussion

The human cornea is highly susceptible to various injuries and diseases that result in scarring, distortion, opacification, and, ultimately, blindness[32]. Corneal opacification is a leading cause of blindness, affecting approximately 2 million people worldwide and accounting for 5% of all blind individuals[33]. In most instances, the best treatment option is corneal transplantation[34,35]. However, this treatment is limited by the scarcity of donor tissues. Fortunately, improvements in regenerative medicine strategies utilizing animal-derived techniques support the development of corneal grafts tailored to individual patients.
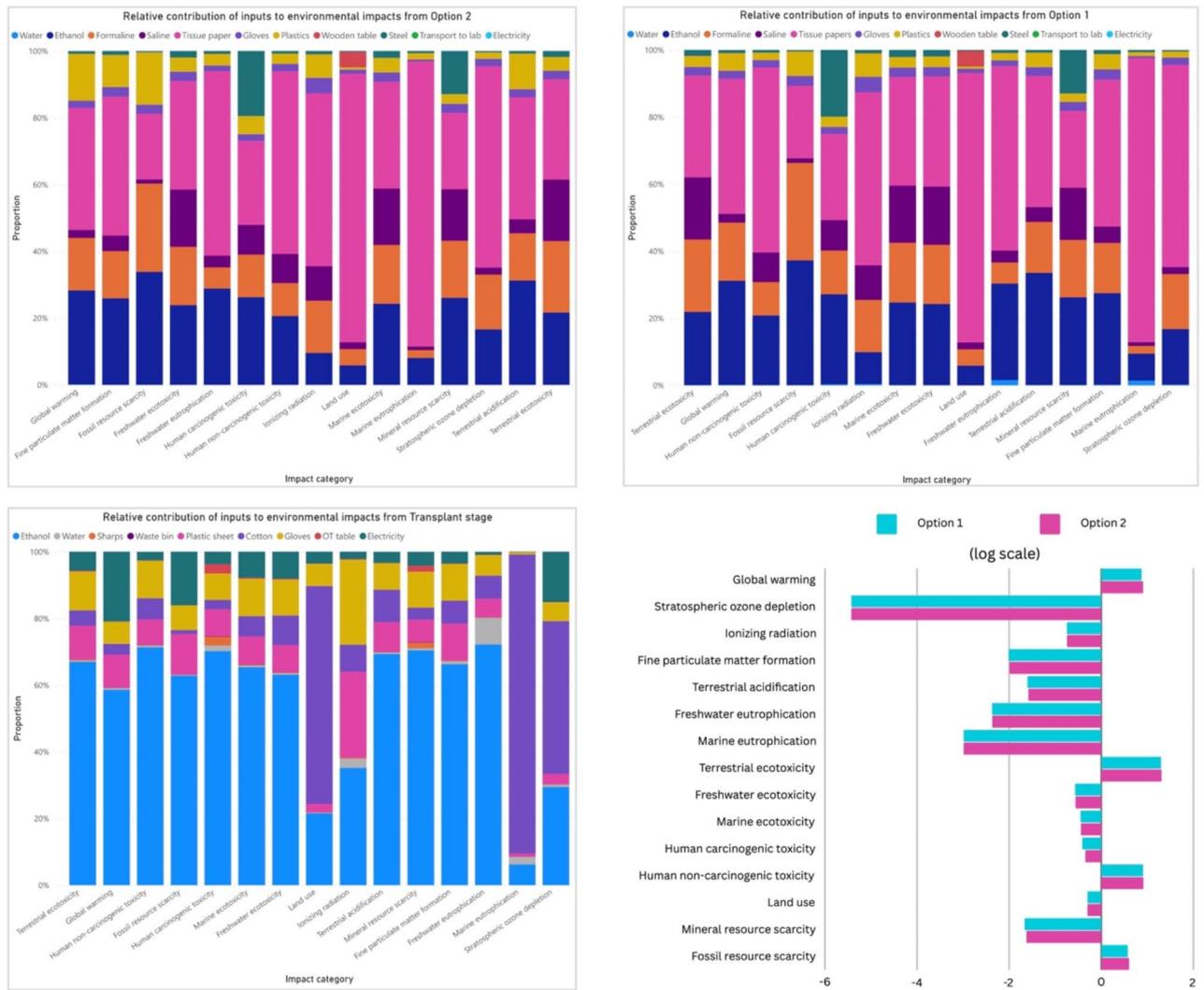
Fig. 3. Midpoint impacts of subcomponents of Options 1, 2 and the transplant stage.

	Option (includes transplant stage)	QALY	Cost (AED)	ICER
Approach 1	Option1	0.04	18705.44	-202,680
	Option 2	0.03	21239.10	
Approach 2	Option1	0.04	18,704	-202,680
	Option 2	0.03	21237.5	

Table 1. Incremental cost-effectiveness ratios for the two approaches.

Ovine corneal xenotransplantation is considered applicable because the eye is regarded as an immune-privileged site. Furthermore, recent non-human primate studies have shown the long-term survival of xenograft for xeno-keratoplasty. As a result, this study focused on a sustainable keratoplasty model based on native corneal extraction from slaughterhouse waste and their tissue-engineered derivatives generated from acellular scaffolds. This approach can potentially produce a virtually limitless supply of corneal xenografts[7].

Slaughterhouses generate billions of tons of biological waste annually[36]. The overwhelming majority of this waste is derived from animals that produce meat for human consumption, while the remainder is mainly unfit for consumption. Livestock most slaughtered for food include avian, aquatic, monogastric, and ruminant animals. Some underutilized remnants, including offals, bones, tendons, and blood, are enjoyed as delicacies in certain countries[37]. Nevertheless, roughly 60% of these remnants become waste that is often discarded at considerable financial/environmental costs[38].

The most common method used to repurpose slaughterhouse waste involves its conversion by rendering plants into industrial by-products such as fats and oils in the form of lard and tallow[39], fertilizers derived from
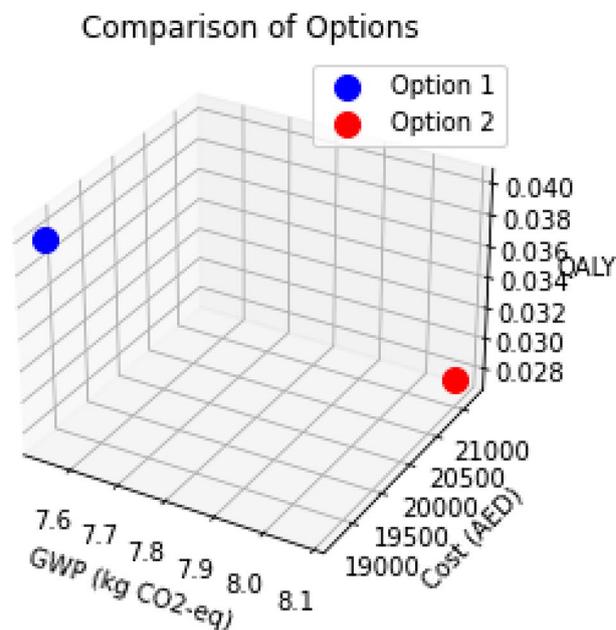
Fig. 4. GWP, QALYs and Costs for Options 1 and 2 (including results from transplant stage).

organic compost[40], biogas through methane production[41], and animal feed as meat powder[42]. Yet, given stricter regulations on the processing of carcasses, rendering has become a less viable option[38]. As a result, alternative methods of managing slaughterhouse waste have been sought to offset current environmentally harmful practices (landfilling, river/ocean dumping, and incineration) and increase their potential utility. To this end, some other uses of discarded byproducts have been investigated, including biosubstrates and biomaterials. In turn, this relatively unexplored use of slaughterhouse waste has devised a new field focused on generating bioartificial tissues and organs from these remnants. Our approach can create the basis for industrial-scale efforts that drive circular economic sustainability and healthcare practices by repurposing slaughterhouse waste in an eco-friendly manner. Eventually, advances in this technology can be translated into comparable decellularized methodologies[43].

Conclusions
Xeno-keratoplasty offers a sustainable source of corneal grafts, reduces reliance on human donors, and promotes circular economy principles within healthcare. This study empirically investigated the environmental and economic impacts of two xeno-keratoplasty procedures: using native corneas and tissue-engineered corneal scaffolds derived from slaughterhouse waste. The findings highlight that the native corneas (Option 1) have a lower environmental impact than tissue-engineered scaffolds (Option 2) due to the additional energy and equipment required for cell culture in Option 2. Similarly, the cost-effectiveness analysis also favored Option 1, suggesting it is both cheaper and more effective at this stage in its technological development.

This study was limited by its single-institution focus, restricting the generalizability of findings to other healthcare settings with different practices and patient demographics. Additionally, the study did not account for long-term environmental and health outcomes, such as the impact of prolonged immunosuppressant use or complications requiring re-transplantation. The life cycle assessment (LCA) also lacked certain critical elements, such as the environmental impact of anesthetics and post-operative care, which may lead to an underestimation of the procedure's true environmental footprint. Furthermore, the cost-effectiveness analysis (CEA) relied on simplified models that omitted potential societal costs, including long-term care and productivity losses. Several assumptions were made to fill data gaps, introducing uncertainty into the outcomes.

Future research should involve multi-center studies to improve the generalizability of results and provide a global perspective on the environmental and economic impacts of xeno-keratoplasty. Additionally, long-term studies tracking both clinical outcomes and environmental impacts, such as extended use of medications and waste disposal, are crucial for assessing the full sustainability of the procedure. Including upstream and downstream medical supply chains in LCA models would further refine the environmental analysis. Advances in tissue engineering, exploring alternative animal models, and a deeper exploration of ethical considerations could help improve both the sustainability and societal acceptance of xeno-keratoplasty. Further research could also integrate more comprehensive health technology assessments (HTAs) that consider patient-centered outcomes and broader societal impacts, offering a balanced evaluation of the procedure's overall value. Overall, this study demonstrates the promise of xeno-keratoplasty as a sustainable and cost-effective approach to corneal transplantation.

Data availability

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M.A.: Methodology, Validation, Visualization, Writing-original draft. P.R.C: Conceptualization, Methodology, Animal Studies. Validation, Visualization, Writing-original draft, Data curation, and Funding acquisition.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

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