From Department of Global Public Health
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Diagnostic assistance to improve acute burn referral and triage

Assessment of routine clinical tools at specialised burn centres and potential for digital health development at point of care

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Assessment of routine clinical tools at specialised burn centres and potential for digital health development at point of care

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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POPULAR SCIENCE SUMMARY IN ENGLISH

Acute burns are a major global health problem worldwide, and those affected are generally the most vulnerable. Most of the cases occur in low- and middle- income countries (like in South Africa) where people are crowded in townships and use open fires for heating, or cooking. Severe burns should be treated in specialised, but rare, centres whereas other smaller burns are best taken care of local clinics. The problem is that acute burns are difficult to diagnose, especially by local doctors and nurses, but the number of specialists is small. This thesis is comprised of four studies aiming at assisting doctors with the diagnosis and the decision to transfer the patient to a specialised burn centre, so that all patients get the best care.

The first two studies were conducted in the South Africa, while the third and fourth studies used specialists and images from both South Africa and Sweden. The first study evaluated the use of a list of referral criteria at admission to a paediatric burns centre. Almost all the patients had at least one criterion, so those who were at the centre should be there. Patients who were older than two and those who had a large burn were more likely to stay longer or undergo surgery than those who were younger than two years or a smaller burn.

In the second study, we looked at the patients who were admitted to the adult burn centre. There, one in five patients who passed away during their stay. The analyses showed that after controlling for other variables, women, those with a large burn, and those who arrived directly to the burn centre were more likely to die during their stay than others. Also, an existing mortality estimation score, "ABSI score", showed that all the patients with a predicted chance of survival smaller than 10% did die. This means that in the future those patients could be treated using palliative care in order to optimise the use of the small resources.

The third study evaluated the ability of specialists to diagnose a burn injury based on images using their smartphone or tablet. The results showed that the size of the burn can be accurately diagnosed by the specialists, and that burn depth was more difficult. However, when looking at whether the burn will need surgery or not, the results were quite good. This can really bring the experts opinion close to the patient, wherever, and whenever they need it.

The problem is that the number of specialists is still very small. In the last study we therefore took one step further by developing an artificial intelligence model using burn images from South Africa and Sweden to find the burn and to classify the need for surgery on its own. The results are still preliminary, and more studies are needed before it can be used for patients but it is a promising solution.

Altogether these results can be used not only for burn injuries, but they are an example of methodologies on how to improve the treatment for all patients by identifying correctly those who will benefit from specialised care and those who can stay close to home. This is particularly true in countries where the resources are small, but also in high-income countries in times of crises such as pandemics when all the patients cannot be admitted for specialised hospital care.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Brännskador är ett stort hälsoproblem över hela världen. De flesta brännskador inträffar i låg- och medelinkomstländer (t.ex. i Sydafrika) där en stor del av befolkningen bor i trångbodda informella bosättningar. Kunskapen hos sjukvårdspersonal (utanför specialistavdelningarna) är ofta bristfällig och både felbehandling samt feldiagnostik är vanligt. För brännskador är den initiala handläggningen viktig för att patienten ska remitteras till rätt sorts vård. Detta för att inte orsaka onödigt lidande och skada för patienten. Patienter med svåra brännskador behöver komma till specialiserade centrum för att få adekvat vård medan andra mindre brännskador bäst tas om hand på lokala kliniker eller vårdinrättningar. Brännskadeexperter är få världen över, både i resursfattiga länder och i resursstarka länder som t.ex. Sverige. Avhandlingen fokuserar på fyra olika verktyg som kan hjälpa läkare att diagnosticera och ta beslut kring specialistvård för brännskador. De första två studierna genomfördes i Sydafrika, medan den tredje och fjärde studien involverade specialister och bilder från både Sydafrika och Sverige.

I den första studien studerades användningen av remisskriterier vid antagningen till en brännskadeavdelning på ett barnsjukhus. De flesta patienter uppfyllde minst ett kriterium vilket innebär att patienterna som var inlagda på avdelningen behandlades på rätt vårdnivå. Sammantaget fann vi ingen skillnad i behandling mellan de patienter som uppfyllde kriterierna och de som inte gjorde det. Däremot hade patienter som var äldre än två år och de med svåra brännskador högre sannolikhet att stanna längre på sjukhuset eller att genomgå operation. Den andra studien tittade på dödligheten på brännskadeavdelningen för vuxna. En av fem patienter dog under sin vistelse. Det fanns en högre dödlighet bland kvinnor, patienter med stora brännskador och de som kom direkt till specialistsjukhusen. Alla patienter som, enligt en gradering för att förutsäga dödlighet, hade en sannolikhet på mindre än tio procent att överleva dog. I den tredje studien undersöktes om specialister kan diagnostisera brännskador utifrån bilder på sin smartphone eller surfplatta. Resultaten visar att storleken på brännskadorna kan diagnostiseras med exakthet av specialisterna men att bedömningen av brännskadedjup var något svårare. För den fjärde studien utvecklades två bildbaserade algoritmer för automatiserat diagnostikstöd kring akuta brännskador utifrån en stor databas med brännskadebilder från båda Sydafrika och Sverige. Den första algoritmen kunde identifiera brännskadorna och den andra algoritmen lyckades att klassificera dessas djup. Resultaten är preliminära och det behövs fler studier innan verktyget kan användas i praktiken men de pekar på en lovande lösning för brännskadediagnostikstöd.

I förlängningen kan dessa resultat innebära ett avgörande steg mot jämlik tillgång till högkvalitativ vård och bidra till en minskning av sociala skillnader i sjuklighet och dödlighet till följd av skador. Därutöver kan många av lärdomarna från denna avhandling användas även vara högst relevanta i höginkomstländer under tider av kris som följer av exempelvis pandemier när alla patienter inte har möjlighet att behandlas inom specialistvården.

RESUME EN FRANÇAIS

Les brûlures sont un problème de santé publique qui affecte tout particulièrement les plus vulnérables à travers le monde, notamment en raison de leurs conditions de vie. De plus, les brûlures sont très difficiles à diagnostiquer par les médecins qui n'en voient pas souvent, et le nombre de spécialistes est limité. Il est important qu'en fonction de la gravité des brûlures, les patients soient transférés vers des centres spécialisés ou traités localement pour les moins atteints. Les travaux de cette thèse consistent à évaluer quatre méthodes plus ou moins technologiques qui permettent d'améliorer le diagnostic et le triage des brûlés depuis les services d'urgences vers les services spécialisés.

Les deux premières études évaluent les patients à l'admission dans deux centres de grands brûlés sud-africains. Les deux dernières études incluent des spécialistes et des images de Suède et d'Afrique du Sud. La première étude consiste à évaluer si les critères de référencement pour transférer les patients vers le centre pédiatrique de grands brûlés sont respectés. De fait, la grande majorité des patients admis possède au moins un critère, mais aucune différence dans le traitement n'est observée qu'ils possèdent un critère ou non. Cependant, les patients de plus de deux ans et ceux avec une brûlure plus large ont plus de chance de rester plus longtemps dans le service ou d'être opérés. Le fait que les patients soient admis d'après les critères de référencement est une bonne chose, mais il se peut que ceux-ci ne soient pas assez restrictifs et qu'il faille les adapter afin de vraiment discriminer les cas les plus graves. La deuxième étude évalue la mortalité dans le centre de grands brûlés pour adultes. Au total un patient sur cinq décède lors de son hospitalisation. En particulier, le risque de mourir est plus élevé pour les femmes, les patients avec de larges brûlures et ceux admis directement au centre. En utilisant un score de diagnostic (« ABSI »), tous les patients qui avaient un pronostic vital de moins de 10% à l'admission sont décédés. Dans le futur, il serait envisageable de proposer à ces patients des soins palliatifs afin de ne pas surcharger les systèmes de santé, et de limiter les dépenses en moyens hospitaliers. Dans la troisième étude, des spécialistes estimèrent un diagnostic de brûlures à partir de photos visionnées sur leur smartphone ou leur tablette. Les résultats montrent que la taille de la brûlure est diagnostiquée très correctement alors que les résultats pour le degré sont plus contrastés. Ce télé-diagnostic est cependant limité à la disponibilité des spécialistes. Afin de répondre à ce problème, dans la dernière étude, deux algorithmes d'intelligence artificielle furent développés à partir d'un grand nombre de photos de brûlures, le premier permet d'identifier la brûlure sur la photo, et le deuxième détermine le diagnostic en terme de chirurgie. Les deux algorithmes obtiennent des résultats encourageants qu'il faudra confirmer.

Au final, ces méthodes sont utiles pour le traitement des brulures, et pourraient être extrapolées à d'autres spécialités qui nécessitent l'avis de spécialistes. Une telle approche permettrait l'amélioration des systèmes de santé par un meilleur triage des patients, même dans les pays développés où c'est notablement pertinent en temps de crise, comme celle de la Covid-19, lorsque le nombre de malades dépasse les disponibilités des services spécialisés et que des décisions sur le transfert ou non de patients sont nécessaires.

ABSTRACT

Background: Inappropriate referral of patients for specialised care leads to overburdened health systems and improper treatment of patients who are denied transfer due to a scarcity of resources. Burn injuries are a global health problem where specialised care is particularly important for severe cases while minor burns can be treated at point of care. Whether several solutions, existing or in development, could be used to improve the diagnosis, referral and triage of acute burns at admission to specialised burn centres remains to be evaluated.

Aim: The overarching aim of this thesis is to determine the potential of diagnostic support tools for referral and triage of acute burns injuries. More specifically, sub-aims include the assessment of routine and digital health tools utilised in South Africa and Sweden: referral criteria, mortality prediction scores, image-based remote consultation and automated diagnosis.

Methods: Studies I and II were two retrospective studies of patients admitted to the paediatric (I) and the adult (II) specialised burn centres of the Western Cape province in South Africa. Study I examined adherence to referral criteria at admission of 1165 patients. Logistic regression was performed to assess the associations between adherence to the referral criteria and patient management at the centre. Study II assessed mortality prediction at admission of 372 patients. Logistic regression was performed to evaluate associations between patient, injury and admission-related characteristics with mortality. The performance of an existing mortality prediction model (the ABSI score) was measured. Study III and IV were related to two image-based digital-health tools for remote diagnosis. In Study III, 26 burns experts provided a diagnosis in terms of burn size and depth for 51 images of acute burn cases using their smartphone or tablet. Diagnostic accuracy was measured with intraclass correlation coefficient. In Study IV, two deep-learning algorithms were developed using 1105 annotated acute burn images of cases collected in South Africa and Sweden. The first algorithm identifies a burn area from healthy skin, and the second classifies burn depth. Differences in performances by patient Fitzpatrick skin types were also measured.

Results: Study I revealed a 93.4% adherence to the referral criteria at admission. Children older than two years (not fulfilling the age criterion) as well as those fulfilling the severity criterion were more likely to undergo surgery or stay longer than seven days at the centre. At the adult burn centre (Study II), mortality affected one in five patients and was associated with gender, burn size, and referral status after adjustments for all other variables. The ABSI score was a good estimate of mortality prediction. In Study III experts were able to accurately diagnose burn size, and to a lesser extent depth, using handheld devices. A wound identifier and a depth classifier algorithm could be developed with assessments of relatively high accuracy (Study IV). Differences were observed in performances by skin types of the patients.

Conclusions: Altogether the findings inform on the use in clinical practice of four different tools that could improve the accuracy of the diagnosis, referral and triage of patients with acute burns. This would reduce inequities in access to care by improving access for both paediatric and adult patient populations in settings that are resource scarce, geographically distant or under high clinical pressure.

LIST OF SCIENTIFIC PAPERS

I. **Boissin Constance**, Hasselberg Marie, Kronblad Emil, Kim So-Mang, Wallis Lee, Rode Heinz, Laflamme Lucie. Adherence to referral criteria at admission and patient management at a specialized burns centre: The case of the Red Cross War Memorial Children's Hospital in Cape Town, South Africa. *International Journal of Environmental Research and Public Health*. 2017. 14(7).

II. **Boissin Constance**, Wallis Lee A, Kleintjes Wayne, Laflamme Lucie. Admission factors associated with the in-hospital mortality of burns patients in resource-constrained settings: A two-year retrospective investigation in a South African adult burns centre. *Burns*. 2019. 45:1462-70.

III. Blom Lisa, **Boissin Constance**, Allorto Nikki, Wallis Lee, Hasselberg Marie, Laflamme Lucie. Accuracy of acute burns diagnosis made using smartphones and tablets: a questionnaire-based study among medical experts. *BMC Emergency Medicine*. 2017. 17(1):39.

IV. **Boissin Constance**, Laflamme Lucie, Fransén Jian, Lundin Mikael, Huss Fredrik, Wallis Lee, Allorto Nikki, Lundin Johan. Development and evaluation of deep-learning algorithms for assessment of acute burns: Potential for front-line emergency care. *Submitted*.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABA	American Burn Association
ABSI	Abbreviated Burn Severity Index
AI	Artificial Intelligence
AIDS	Acquired Immuno-Deficiency Syndrome
AUC	Area Under the ROC Curve
CI	Confidence Interval
CNN	Convolutional Neural Networks
DICOM	Digital Imaging and Communications in Medicine
DL	Deep Learning
ECSA	Emergency Care System Assessment
EM	Emergency Medicine
HICs	High Income Countries
ICC	Intraclass Correlation Coefficient
ICT	Information and Communication Technologies
ICU	Intensive Care Unit
LMICs	Low- and Middle- Income Countries
mHealth	Mobile Health. The use of mobile devices for health purposes
ML	Machine Learning
OR	Odds Ratio
rBaux	Revised Baux
Red Cross Hospital	Red Cross War Memorial Children's Hospital
ROC	Receiver Operating Characteristic
SDGs	Sustainable Development Goals
TBSA	Total Body Surface Area
WHO	World Health Organization

INTRODUCTION

The recent Covid-19 pandemic has been illustrative of the important coordination between emergency care services and critical care services when under pressure. It has also highlighted the need for improving digital health solutions in order to provide care to all, even those in isolation or at a distance who could not be transferred from one healthcare centre to the other. Burn injuries affect the very poorest of the populations, and are usually associated with terrifying stories behind each patient, however they are also require one of the most specialised and comprehensive care. Improving the care for all patients by directing the patients to the right level of care has been a true driver. Also, as an independent researcher, I aimed to alleviate the high workload of those very limited but extremely generous specialists so that each patient can be treated using all possible resources. Of course the work in this thesis was designed (and almost finished) by the time the pandemic had hit, but I believe that the evaluation of the different methodologies assessed, and the various outcomes measured can be beneficial not specifically for the treatment of burns but that the lessons learnt can be extrapolated to other medical fields and to apply to all settings. Together, they have the potential to reduce inequities in a wide range of areas and results obtained in low-resource settings definitely resonate with needs of under-pressure healthcare systems even in high-income countries.

I wish the energy, the never-ending commitments of burn experts and the hopes of all the patients I have crossed along my way will be reflected in this work. It is a dedication to all those who have crossed my path, who could have, or who will, in one of those endless hospital corridors.

BACKGROUND

Accurate diagnosis and triage in a global health context

Current status of emergency care and access to specialised care

In 2019 the World Health Assembly adopted the resolution "*Emergency care systems for universal health coverage: ensuring timely care for the acutely ill and injured*" that highlighted the importance of timely and accurate diagnosis and care to reduce both morbidity and mortality worldwide [1]. High quality care involves all steps from access to care, accurate assessment of the condition and comorbidities, appropriate and timely treatment, as well as referral to a hospital when specialised and surgical care are needed [2]. Furthermore, high quality health systems are needed to respond not only to every day challenges, but also be resilient in order to be prepared for – and respond to – acute crises, in addition to routinely high demands of patient care [2].

Large discrepancies can be observed between high-income countries (HICs) and low- and middle-income countries (LMICs) in access to care, as well as in the care received from initial emergency care to post-surgical care. It has been estimated that a total of eight million people die each year in LMICs from conditions treatable by the health system, and out of these, three million lack access to care altogether, while the other 60% die of poor-quality care [2]. For emergency care, estimates indicate that about 24 million lives are lost each year in LMICs (representing just above half of the deaths) due to conditions that could potentially be addressed by emergency medical care [3, 4]. This can be exemplified by the comparison of the median mortality rate in emergency departments, which is 45 times higher across 65 LMICs than that observed in American emergency departments, a number reaching 85 times higher when only considering Sub-Saharan African countries [2, 5]. Further, modelling studies estimate that between 20 to 38 percent of the global injury burden (representing between one and two million fatalities each year) could be averted if severe injury outcomes in LMICs were similar to those in HICs [4, 6]. Similarly, although the population seeking both emergency and surgical care in LMICs is typically younger and without any chronic conditions – which is very different from the patient load in HICs – there is a higher burden that can reach twice the risk of dying post operatively in African countries compared to HICs [5, 7]. This segment of the population is also often comprised of economic earners. This thus has financial and social consequences for whole communities beyond just the injured [8].

Unfortunately, initial emergency care in LMICs is most often provided by lay people, or by frontline providers who are not doctors and who have to act with very limited diagnostic resources [4]. It has, however, been postulated that simple interventions to facilitate triage as well as communication and supervision of junior medical providers could reduce the mortality attributable to inappropriate emergency care by about half [5]. Indeed, following the implementation of the World Health Organization (WHO) Emergency Care System Assessment (ECSA) tool in 25 LMICs, one of the six areas targeted for priority action in order to improve emergency care services was the development and dissemination of triage and condition-specific management tools [6, 9, 10].

After the provision of initial care at local clinics or rural/district hospitals, patients are often referred to central or tertiary hospital for specialised care; however, these transfers can be inappropriate and can increase the workload, the burden for the health system and the patient, as well as diminish the workflow [11]. Especially in LMICs, point of care providers and emergency physicians have to deal with almost all medical and surgical conditions and are located in vast geographical areas [12]. Specialised care – if available – is on the other hand usually confined to major cities and the expert knowledge is therefore of limited access to most patients. A referral is consequently needed and is defined as "*any process in which health care providers at lower levels of the health system who lack the skills or the facilities to manage a given clinical condition seek the assistance of providers who are specially trained to guide and take over the responsibility of a patient*" [13]. Effective patient transfer from point of care to specialised care relies on the health system organization, but also on the compliance of health care facilities and providers to follow protocols and processes in place in order to reduce inappropriate system use [14]. The need for specialty referral has been an existing source of frustration for many decades, for health care providers at point of care, specialists, and also for the patients. These frustrations include lack of communication between providers, unavailability of patient medical records and inappropriate follow-up, together with the associated time and energy wasted. In HICs this has led to the development and implementation of referral guidelines as a gatekeeping mechanism to improve this practice [15]. Referral guidelines can provide a foundation for the improvement of the referral process by delimiting which conditions should be referred for specialised care while also defining those that can be managed by point of care providers [15]. The development of information and communication technologies (ICT) in the past few decades have been considered in healthcare in order to reduce the number of unnecessary referrals by allowing for specialists assist with triage decisions by pre-screening referrals prior to transfer. These technologies are nowadays included in the definition of digital health.

Digital health: new opportunities for remote diagnosis

According to the WHO, digital health is defined as "*a broad umbrella term encompassing eHealth (which includes mHealth), as well as emerging areas, such as the use of advanced computing sciences in 'big data', genomics and artificial intelligence*" [16]. In May 2018, the World Health Assembly adopted a *Resolution on Digital Health* where it mentions the value of digital technologies for advancing both universal health coverage and the health-related Sustainable Development Goals (SDGs) [17]. In order to improve the quality of care this includes provider-to-provider telemedicine. Telemedicine permits "*the consulting with other health workers, particularly specialists for patient case management*" and clinical decision support systems, for example using "*algorithms to support service delivery according to care plans and protocol*" [16]. Both the WHO Regional Office for Africa and the United Nations have signed an agreement to enhance healthcare in Africa with the use of digital technologies in order to develop sustainable and cost-effective systems to provide equal access to healthcare on the African continent using mobile phones [18]. Until recently LMICs could not benefit from these informatic innovations due to the high cost of electronic devices, absence of appropriate mobile connectivity and limited user literacy in those devices [19]. However, digital health has grown tremendously in the past couple of years globally, in combination with the unprecedented rate of smartphone penetration. At the end of 2019 there were about 500 million subscribers to mobile services in Sub-Saharan Africa, of which over 50% were using smartphones. This trend is likely to continue with an estimation that this number will double within the next five years [20].

The development of mobile devices, together with the involvement of healthcare professionals and specialists, has led to the spontaneous development of informal transfer of patient information and images between point of care and specialists to respond to a clear need in rural and distant areas [19, 21]. Thus, mHealth has the potential to reduce inequities by providing rural or distant clinicians with specialist consultations for affordable price, in order for specialists to diagnose, triage and assist with complex cases thereby avoiding lengthy waiting times and inappropriate referral [22-26]. The saying "*a picture is worth a thousand words*" is also true in healthcare [27] and it is the specialties based by nature on visual assessment which have benefited most from image-based remote consultation to improve triage decisions. These include dermatology [28], plastic surgery [24, 29, 30], pathology [31], and injuries [32, 33].

A further step has been made in the field of medical image analysis, combined with the development of artificial intelligence for image analysis, in particular with the application of machine learning and deep-neural networks [34]. Figure 1 describes the connection between artificial intelligence (AI), machine learning (ML), deep learning (DL), and convolutional neural networks (CNNs). Artificial intelligence concerns the ability of a computer to mimic human thinking by interpreting and learning data to make decisions. Machine learning is a subset of artificial intelligence whereby the algorithms are created by acquiring knowledge from historical examples. Deep learning uses self-trained algorithms to perform a task by exposing multi-layered neural networks to large amounts of data.

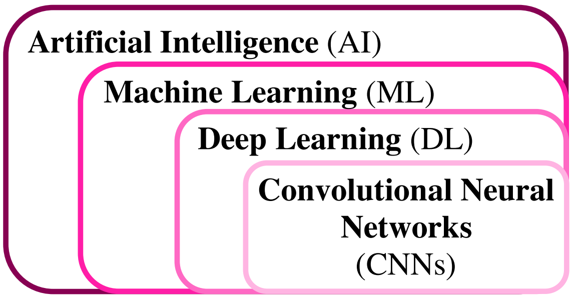


Figure 1. Connection between artificial intelligence, machine learning, deep learning and convolutional neural networks.

Convolutional neural networks are currently the leading tool in computer vision and image analysis [35]. Their principle for image-based analyses are presented in Figure 2. The input image is used to form kernels (or filters) which identifies features such as shapes, edges, or colours regardless of their location in the image, in order to output a feature map which is then fed as an input for the next convolutional layer. The layers can then be transformed using non-linear functions in order to identify even more complex features. Pooling layers are also used to perform down-sampling of the input in order to reduce its dimension. Once all features have been extracted, they are fed into a fully-connected network for classification of the output [36].

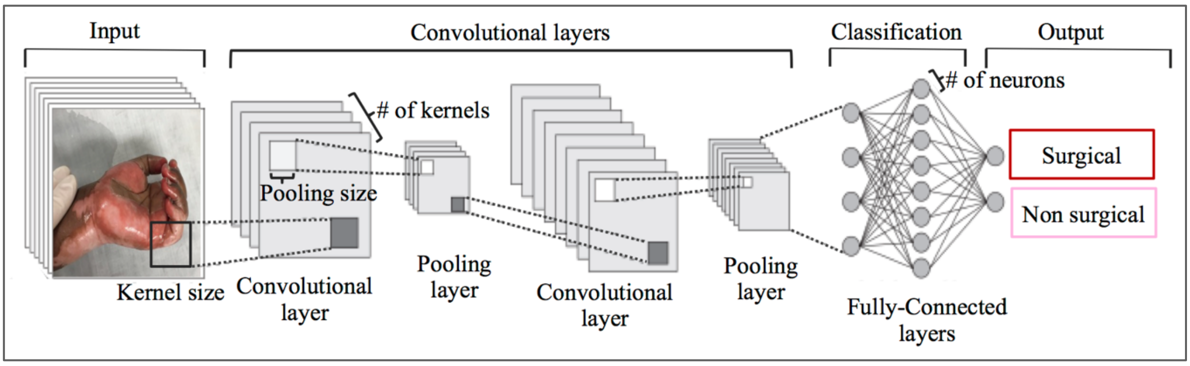


Figure 2. Schematic representation of image classification using CNNs (adapted from [36]).

After being used for general visual tasks such as object recognition [37], there has been a tremendous development of CNNs in healthcare in the recent years [38]. Here again, it is the disciplines where visual interpretation is key and where large amounts of annotated data could be collected that have mostly benefited from these advancements: dermatology [39], ophthalmology [40], radiology [41], pathology [42], cardiology [43] and even plastic surgery [44, 45].

Burn injuries are used in this thesis as an example for the application of these different tools for diagnosis, referral and triage as 1) they are relatively common, especially in resource-scarce settings; 2) they are of visual nature but difficult to diagnose for the untrained clinician; and 3) referral and transfer of severe burns require transfer to specialised centres to decrease burn mortality while minor burns should be treated at point of care.

Burns – a challenging trauma for diagnosis which requires specialised care

Global burden of burn injury

Burn injuries are defined by the destruction of tissues – whether it is the skin or other organs – due to energy transfer which is caused in most cases, by heat through flames, hot liquids (scalds), or hot solids (contact burns), but it could also be caused by friction, cold, radiation, electricity or chemicals [46]. According to the latest data report in 2016, burns were the fourth largest cause of injury deaths worldwide with approximately 418 deaths a day, or 153,000 deaths annually [47]. The share of this burden is however unequally divided globally, with the burn death rate three times higher in LMICs compared to HICs [48] and

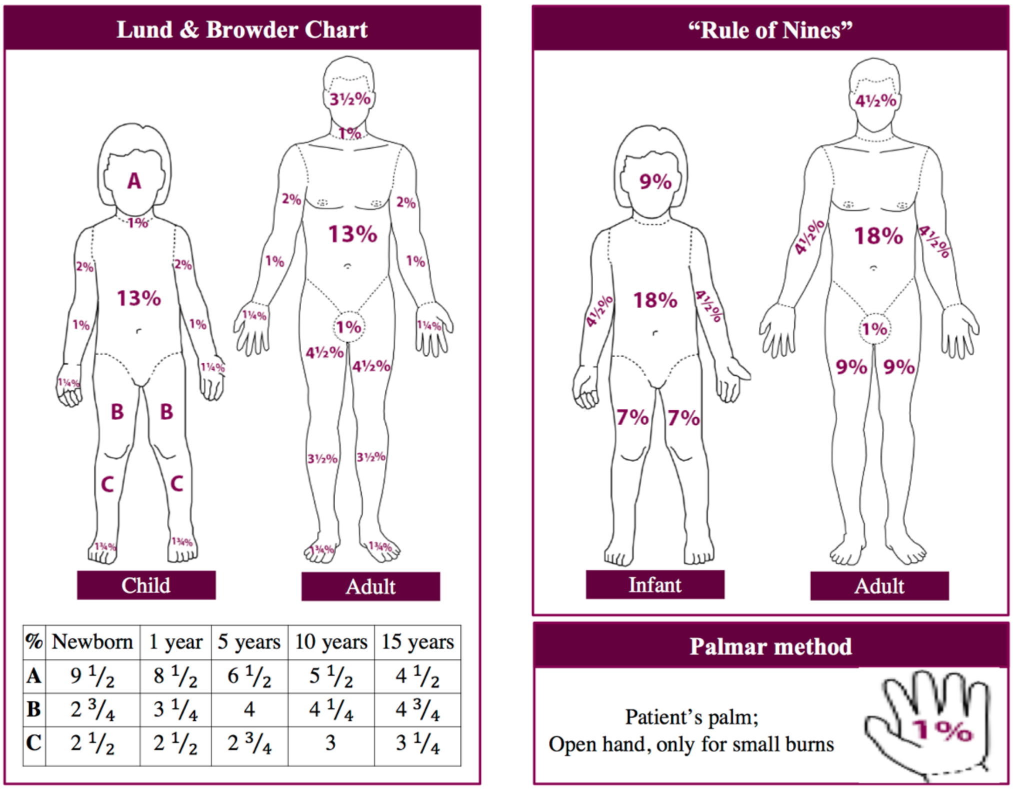
94% of the burns-associated deaths occurring in LMICs [49]. Slightly over a third of those deaths occurred in the WHO defined South East Asian region whereas another 30% occurred in the African region [47]. Similarly, deaths of children one to fourteen years of age is 7.5 times higher in the Sub-Saharan region than in HICs [50].

This thesis was conducted in South Africa and Sweden. In South Africa there is an estimated 1.6 million burn injuries each year, of which 8,000 are admitted to burn specialised services [51]. Reported age-adjusted mortality rates throughout the country vary from 4.8/100,000 inhabitants in rural areas [52] to 7.9/100,000 in the metropolitan centre of Cape Town [53]. Further, according to a recent evaluation in one of the country's urban mortuaries, approximately three percent of deaths were due to burns [54]. In comparison, in Sweden, an average of approximately 1,500 patients were admitted to hospitals for burns injuries during years 2000-2014, and the latest reported mortality rate was of 0.7/100,000 [48].

Burn incidence and mortality vary not only between countries, but also within countries, with variations observed between socioeconomic status, gender, age, ethnicity and place of residence [55]. Poor living conditions [56-58], low income [59-62], and immigrant status [63-65] have all been described to be associated with higher rates of burn injuries. In resource-scarce settings this may have to do with lack of access to modern energy – which is estimated to 13% of the world's population [66] – and to overcrowded smaller shelters [67]. Regarding age groups, there is a higher prevalence in young children globally [54, 68-74]. In adulthood there is a difference in prevalence with a peak in the elderly seen in HICs [46, 70, 71] that is not always seen in LMICs [53, 75, 76]. Contrary to the general trends for injuries in general where men are most often affected [77], there is currently context-specific mixed results with regards to gender distribution in burns prevalence. Women mortality represents 55% of the global number of deaths [47] and higher prevalence rates are reported especially in South-East Asia [75, 78, 79] where the traditional role of women in cooking could be an explanation [80, 81]. On the other hand, men have been most commonly affected according to reports in other settings [54, 55, 69, 82-85].

Burn pathophysiology and estimation of extent and thickness

Besides its cause, a burn is defined by its severity which includes both its extent and its depth. The burn injury's size is defined as the total body surface area (TBSA) affected and is essential in the calculation of the Parkland formula which is commonly used to estimate fluid volumes for patient resuscitation [86]. In patients with major burns (usually over 15% in adults [87]), lack of, or inappropriate, fluid resuscitation will lead to burn shock while over-resuscitation can also be dangerous, leading to compartment syndrome, injury complications and deaths [88, 89]. It is therefore critical to have an accurate TBSA estimation. To obtain this, a number of estimation methods have been suggested (see Figure 3), which include the Lund and Browder chart [90], the "Rule of Nines" [92], and the palm percentage estimation [94].



%	Newborn	1 year	5 years	10 years	15 years
A	9 1/2	8 1/2	6 1/2	5 1/2	4 1/2
B	2 3/4	3 1/4	4	4 1/4	4 3/4
C	2 1/2	2 1/2	2 3/4	3	3 1/4

Figure 3. TBSA estimation tools. (adapted from the Lund & Browder chart [90,91], the "Rule of Nines" [92,93], and palmar method [94]).
The estimations presented are for the anterior part of the bodies. Similar proportions need to be used for the posterior part. For the Lund & Browder chart, buttocks count's for 5%.

Despite the use of those estimation tools, there is a large body of evidence that burn size is often miscalculated ([95-105]). The most common error is overestimation, especially for burns in children and smaller burns, whereas larger burns are more likely to be underestimated [103]. Moreover, a study from an American burn centre showed that the further away in the referral chain the larger the error in diagnosis, with emergency medicine services' staff overestimating burn size by 40%, referring physicians overestimating burn size by 19% and doctors working in the emergency department of the burn centre's hospital overestimating burn size by seven percent [99].

Burn depth assessment affects the patient's treatment, particularly whether a wound should be surgically excised or not. Depth is anatomically classified into five categories: superficial thickness, superficial-partial thickness, mid-partial (or indeterminate thickness), deep-partial thickness and full thickness [106]. Depth is currently further divided into two categories based on surgical treatment strategies: partial injuries that include superficial-partial thickness through mid-partial thickness burns, and deep injuries that include deep partial thickness and full thickness burns (See Figure 4) [107]. Superficial burns only affect the uppermost layer of the skin (epidermis), such as sunburns, are typically benign and heal within two to three days. Superficial- and mid-partial thickness burns extend down to the capillary dermis and usually form painful blisters. They form wet, pink wounds that blanch when pinprick, and will heal spontaneously within two weeks even if they may scar. Deep partial thickness wounds extend to the reticular dermis and might involve the destruction of some pain receptors. They are therefore less sensitive to pain, or blanching and appear whiter once blisters are removed. They will take over three weeks of healing and therefore will involve scarring and surgery. Finally, full thickness burns involve all the dermis and might extend to underlying tissues such as muscle or bone. They usually present with almost no pain and are insensitive to touch. They will not heal spontaneously and will require surgery. In summary, while superficial thickness, superficial-partial and mid-partial thickness burns will heal without surgical intervention, deep partial thickness and full thickness burns will need to be surgically excised and autologous skin grafted in order for them to heal [46, 107].

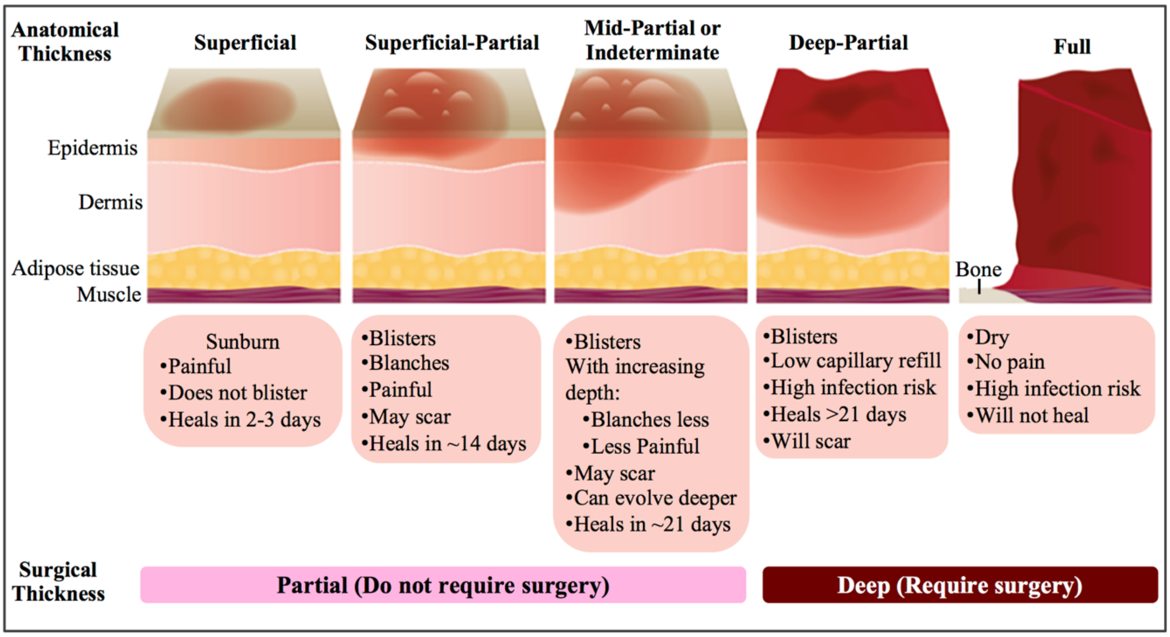


Figure 4. Schematic representation of burn depth (adapted from [46, 108]).

A burn is, however, an evolving element and this increases the complexity of the diagnosis [109]. The most widely reported used technique for burn depth estimation is through visual assessment which can be enhanced by tactile (pain, blanching and moisture content) information [110-112]. This method is still the current gold standard; however, it is subjective, and relies highly on training, experience and expertise [113]. Indeed, while very superficial and deep burns are usually accurately diagnosed, intermediate burns are a cause of more complex diagnosis [110]. Accuracy rates among burns surgeons at entry to burn centres range from 62% to 89% [114-120]. Although of high clinical relevance, burn depth at emergency centres are often neither reported [121], nor accurate is the diagnostic ability of referring physicians which is expected to be even lower than those of burns surgeons at about 51% [122]. A number of alternative solutions have been suggested and investigated in order to define more objectively burn depth and areas which would benefit from early surgical excision and grafting [123]. These include invasive methods such as repeated biopsy and histology [124], and other less invasive methods like thermography [125], laser doppler imaging [126], laser speckle imaging [127], optical coherence tomography [128] and multispectral imaging [122] among others. Although these methods might prove high accuracy levels, their adoption has been much slower than expected and their use have not been widespread due to a number of reasons. This includes high costs, bulkiness of the instruments, and lack of user-friendliness [122, 129]. According to the American Burn Association "*An ideal or optimal method [for burn depth diagnosis], which is non-invasive, simple, rapid, cost-effective and accurate, as early as possible after the injury, remains elusive*" [130]. Most of the above-mentioned technologies can be helpful only 48 hours to 5 days post burn [129, 131] and usually require debridement of the wound prior to being evaluated [132]. Solutions for improved diagnosis of burn depth at point of care in the hours following the injury remain therefore necessary.

Routine clinical triage tools at specialised burn centres

Triage is the "*sorting of patients for treatment in situations of at least modest resource scarcity, according to an assessment of the patient's medical condition and the application of an established sorting system or plan*" [133]. Triage might involve the selection of patients for referral, admission to burn centres, or discharge. Furthermore, triage might be used to prioritize the care of patients who have the greatest chance of survival [134]. In settings where burn centres are well-equipped and the number of patients is manageable, the questions pertaining to triage might relate solely to which patients to transfer via air services rather than by the road [135-138]. In settings where resources are scarce the relevance of patient treatment as a whole can be questioned [139]. It has been proposed that under resource constraints, burn management in LMICs can be compared to that of disasters' management in other settings [134, 140]. In that case, triage promotes the benefit of the whole population rather than the benefit of the individual patients. This might mean denying treatment to the severely injured who may have been salvaged with numerous resources, but which would have died anyways if there are too many patients and too short resources [134].

The ultimate aim is to reduce both under and over triage. Under triage leads to delayed treatment and increased morbidity and mortality; over triage leads to the unessential referral and treatment and, as a consequence, unnecessary use of limited resources [137]. Several clinical tools have been developed for usage at point of care or at admission to burn centres in order to better discriminate those patients who would benefit most from the specialised care [141]. Apart from general trauma scores assessing airway, breathing, cardiac status, disability and neurological deficit [141]; these include referral criteria developed to assist with referral and transfer of patients for admission to burn centres and composite mortality prediction models which can assist with difficult decisions such as futility at the burn centres.

Referral Criteria

The American Burn Association established a set of referral criteria for burn centre referral in the 1990s with the aim to "*both assist referring clinicians with triage decisions as well as to improve delivery of burn expertise to burn patients*" [142, 143]. Similar sets of criteria have been adapted to the contexts and developed in several other regions including Australia and New Zealand [144], and Europe [145], but also in a few LMICs including Turkey [146] and South Africa [147]. Several of the criteria are similar across contexts such as those of burns on sensitive body parts (for example the face, the hands, or the genitalia), or the presence of existing comorbidities. There are however differences in others. For example, whereas the burn size suggested for referral in Denmark is three percent [137], the high prevalence of burn injuries in South Africa leads to a referral criterion of burn size of 15% in children and 25% in adults [93]. Once these criteria are in place, it is important to assess how well they are followed throughout the referral chain. Adherence to referral protocols has been evaluated in a few studies, but almost all are from high income settings [102, 121, 135-137, 146, 148-158]. These studies can further be divided into two groups: those that considered the situation at emergency departments or referring centres [121, 148-153], and those considering the situation at the burn centres [102, 135-137, 146, 154-158]. Whereas the former studies give an insight in both under and over triage, the latter shed light on whether all patients admitted are in adherence with the criteria in place, and whether the resources at the burn centres are used to their full potential. In some settings the number of patients that are not referred to a burn centre in spite of meeting the referral criteria can be high. This is the case in the United States [149, 153], and in the United Kingdom [148]. This has also been demonstrated at other levels of care – from pre-hospital emergency services all the way to the trauma centres of tertiary hospitals – in the Western Cape of South Africa, the setting of the current studies [121, 152, 159, 160]. On the other hand, the evidence accumulated thus far from burn centre studies indicates that adherence to the referral criteria at admission is not optimal and varies greatly between settings. For example, studies in American burn centres report adherence ranging from 55% in a paediatric unit [155] to 100% in a Texan burn centre accepting patients of all ages [135]. In resource-scarce settings there are also wide variabilities, for example in Iran only 34% of the patient transferred met the referral criteria [158], whereas in a Malawian central hospital, burns had the lowest rate of over-triage compared to other traumas with 69% of the patients accurately referred [11]. Over triage of the patients can lead to excessive costs. For example, in a Danish study, a fourth of the patients transferred from a referring site using a helicopter did not adhere to the referral criteria [137]. In a Canadian burn centre, 24% of the transfers were deemed unnecessary, and their associated costs was of 200,000 Canadian dollars for transport alone [136]. In fact, for some of those patients, air transport can even exceed hospital charges [138].

Another concern with regards to the optimization of resources is the transfer of futile patients. Futility can be defined as "*the threshold at which, with a high degree of certainty, goals of care cannot be met at any time, and further efforts to reach these goals are not warranted*" [141]. Even in HICs their transfer, often via air transport, can have high costs for the healthcare system (estimated to 30,000 Canadian dollars). In settings where resources are even more scarce, this can have larger consequences, not only by overloading the burn capacities, but also for the individuals' families which might be impoverished by repatriating the body to their community [161].

What is currently known:

- Referral guidelines for burns care to specialist services have been developed in a number of settings but are rarely assessed
- When assessed at admission to burn centres in HICs, there is usually an over triage of patients and criteria are not optimally adhered to
- In the Western Cape of South Africa, a large number of patients adhere to referral criteria at lower levels of care, but are not transferred to the burn centres

Knowledge gaps:

- No studies have evaluated the adherence to referral criteria at admission to burn centres in a ressource-scarce setting
- The relation between adherence to referral criteria and patient management at the burn centre is unknown

Box 1. Referral criteria for transfer of patients to burn centres (Study I).

Mortality prediction scores

In order to best define who will benefit most from the specialised care provided, it is also important to look at the outcome of burn patients once they are admitted to the burn centres. Mortality prediction scores are based on key factors associated with an increased risk of mortality and can ultimately assist with identifying patients for whom intensive care would be futile [162-164], so as to spare the limited available resources for those who are likely to benefit the most from them [139, 165]. When burn centres operate at full capacity with demands exceeding the bed availability, as it is in South Africa, complex decisions regarding which patient to admit must be based on anticipated prognosis that have been developed or verified in that specific context [166]. In order for prediction models to assess the probability of death prior to admission, or even referral, it needs to be based on patient and injury factors that can be assessed easily and objectively [167].

In the early 1960s, Baux was the first to establish a mortality prediction score by adding patient age and burn surface [168]. Later on, some models even added to this initial one inhalation injury [169-171]. Using those characteristics and others such as burn depth [172-174], presence of comorbidities [175, 176], or gender – although more controversially – [171, 177, 178] several additional prognostic scores then emerged in the past few decades (reviewed in [179, 180]). One review from 2013 identified only eight models which fulfilled all methodological standards for both construction and validation [179]. Of these, two are most often used in clinical practice: the revised Baux score (rBaux [170]) and the Abbreviated Burns Severity score (ABSI [181]). The rBaux is easily calculated by:

$$Age + \%\,TBSA + 17 * (if\ inhalation\ injury\ is\ reported)$$

and its inverse logit transformation is then used as a strong precision of mortality prediction [170]. The ABSI score is even easier in that it does not require any advanced calculation and is obtained by adding scores assigned to five predictive variables at admission (see Figure 5): sex, age, inhalation injury, burn depth and TBSA [181].

Variable	Patient / injury characteristic	Point
Sex	Male	0
	Female	1
Age in years	0-20	1
	21-40	2
	41-60	3
	61-80	4
	81-100	5
Inhalation injury	Absent	0
	Present	1
Full thickness burn	Absent	0
	Present	1
TBSA burned (%)	1-10	1
	11-20	2
	21-30	3
	31-40	4
	41-50	5
	51-60	6
	61-70	7
	71-80	8
	81-90	9
	91-100	10

ABSI score	Threat to life	Probability of survival
2-3	Very low	≥99%
4-5	Moderate	98%
6-7	Moderately severe	80-90%
8-9	Serious	50-70%
10-11	Severe	20-40%
12-13	Maximum	≤10%

Figure 5. Abbreviated Burns Severity Index (ABSI) score as previously defined [181].
It is calculated by adding the total number of points for each of the five variables; which then provides an estimation of the patient's survival probability (right panel).

Like most of the other suggested prediction scores, the ABSI was developed in 1982 in a HIC, in this case the United States, and has since been validated in other high-income settings [182, 183]. Variations in resources and patient-load require verification of the scores' accuracy to each differing setting. As a matter of fact, it has recently been validated in a number of burn centres from LMICs including in Malaysia [184], Indonesia [185], and Ghana [167]. The wide heterogeneity in groups of patients between countries and burn centres does not allow a "one size fits all" prognostic tool and therefore individual burn centres have recalibrated scoring systems to their own patient populations prior to use for appropriate allocation of care [166, 180]. For example, results from a Kenyan [186] and a South African [187] burn units showed the original ABSI score had to be modified in order for mortality breakpoints to better represent the studied populations.

<u>What is currently known:</u>

- The state of knowledge regarding patient and injury characteristics associated with in-hospital mortality in specialised burn centres as well as established mortality scores are mostly based from HICs, and are rarely evaluated on different patient populations
- This would be required prior to utilization at admission for resource allocation and triage

<u>Knowledge gaps:</u>

- The level of mortality and its associated characteristics at admission to a specialised burn centre in South Africa is unknown
- It is unclear whether a prognostic model such as the ABSI score provides accurate mortality predictions at admission to a South African specialised centre

Box 2. Mortality prediction scores in burn care (Study II).

Although the ultimate prediction score will be based on easily identifiable and interpretable injury characteristics, it is paramount that the initial diagnosis is as accurate as possible.

Digital health and acute burns remote diagnosis

Remote consultation by clinical specialists

Recent updates of national referral guidelines – for example in France or the United States – now recommend the use of "telemedicine" between point of care providers and burn specialists as a standard procedure prior to any transfer [91, 142]. The specialty lends itself to both synchronous or real-time videoconferencing and asynchronous "store-and-forward" sharing of images between point of care providers and specialists [23]. Telemedicine has been used in various ways for the provision of burn care. For example, live assessment of the injury with videoconferencing for severity evaluation [188, 189], use of images prior to patient transfer [190, 191], transmission of images for surgery estimation [192], video assistance during the surgical procedure [193], to wound closure [194] and patient home-care follow-up [195, 196]. Notably, the accuracy of photograph-based diagnosis of burn injuries has been proven already for a number of years [197-202]. Reports from the outcomes of the transfer of images on the referral and admission of patients in burn centres show impressive results [191]. For example, in the United States 24.5% of the initial transfer decisions were changed [191]. Similarly, when using videoconferencing, 364 acute patient transfers were avoided in an Australian burn centre over an eight-year period [203]. These practices have been in place for a large number of years in HICs, as exemplified by a survey performed in the United States in 2012 where 84% of burn centres reported using telemedicine [204]. Yet, the spread of these practices were limited in LMICs until recently due to the necessary use of advanced, bulky and expensive devices. In recent years however, the introduction of mobile devices, and more specifically of smartphones, has brought new opportunities. For example, the smartphone penetration in South Africa which was 46% of the population in 2016 dramatically increased to 91% in 2019 [205]. With that, burn care in the country organised itself around the introduction of communication between point of care providers and burn specialists [190, 206, 207]. These initiatives first used the potential offered by informal social networks, such as WhatsApp for communication [190, 206], and more organized ventures were thereafter also implemented (named Vula and brought about as part of a collaborative project between researchers at Karolinska Institutet and Stellenbosch University [207]). The transmission of images with burn specialists resulted in avoiding 38% of inappropriate transfers to one burn centre in Kwa-Zulu Natal [190], or in avoiding 150 admissions over an 18-months period in the Western Cape's paediatric burn centre [206]. These positive results are however balanced by the challenges observed in the implementation of a more formal initiative [208]. Whereas the potential health impact of diagnostic devices is usually best assessed using randomized control trials, this might not be possible when considering the development of tools for acute burns diagnosis in low-resource settings [208]. Thorough evaluations of methods should however still be considered prior to implementation and use in healthcare. This has particularly been an issue with mHealth development in LMICs which were not adequately assessed [209, 210].

The American Telemedicine Association Guidelines for Teleburn specify that "*image quality is essential for teleburn consultation including accurate diagnosis and treatment recommendations*" [23]. It also defines a number of prerequisites for image quality in store-and-forward image capture and analyses such as the use of a digital camera rather than cell phone camera or the of displays with a minimum resolution of 1280x1024 pixels for assessment of the images [23]. This does not fit the current practices that make use of the specialists' smartphones or tablets, especially in contexts where computers are probably less available than mobile devices. As part of the implementation project in South Africa, the acceptable quality of smartphones to capture images [211] as well as that of handheld devices to view images [212] has previously been investigated. In other medical fields the use of devices that were not adapted to the "digital imaging and communications in medicine" (DICOM) standards has been debated as it might be suboptimal for diagnosis. In dentistry for example, tablets showed lower diagnostic accuracy [213, 214]. In radiology where extensive research has been performed, there were contrasting results with tablets usually showing satisfying results which was not always the case with smartphones [215-222]. On the other hand in dermatology and ophthalmology, smartphones were acceptable devices with regards to diagnostic accuracy [223-225].

<u>What is currently known:</u>

- Burn experts can diagnose a burn on a computer screen or on printed photographs, but the accuracy level depends on expertise and country of practice
- In other medical fields handheld devices such as tablets have also been used for establishing a diagnosis
- In the recent years, burn diagnosis using smartphone consultation has been taking place globally without formal evaluations of the outcomes

<u>Knowledge gaps:</u>

- The accuracy of the diagnosis for acute burn injuries given by experts using handheld devices is of sufficient quality has yet to be evaluated
- Too little information exists with regards the ability of different groups of burn specialists (with different backgrounds) on their ability to accurately diagnose the injury

Box 3. Diagnostic accuracy of image-based remote consultation (Study III).

Potential for automated burn diagnosis

Although the use of remote consultation for burn injuries is recommended, and already taking place in a number of settings, its development is limited by the availability of burn specialists who are already in short supply and are not able to handle all cases [226]. With the development of deep learning in the medical field, it is possible that automated diagnosis can be a potential solution to alleviate both the number of cases reviewed by the specialists and increase the access to diagnosis for patients. Indeed, the use of automated burns size calculations has been suggested using mobile apps [227-229]. Regarding burn depth, the first attempts to develop an automated algorithm date back to over fifteen years ago and identified psychophysical characteristics that were then manually used for machine learning development [230-232]. More recently, some deep learning algorithms have been used to distinguish small areas between burns and other types of wounds [233, 234] or normal skin [235-237]. The most complete and up-to-date algorithm for the determination of burn depth used 23 images and obtained an accuracy of approximately 80% when categorizing wound parts into six categories, including non-burnt skin [238]. Most of these studies used patients with light skin types and only one recent study included patients from an African country (Nigeria), which indicated the complexity of training a combined model for all skin types [235].

<u>What is currently known:</u>

- Burn areas can be classified from healthy skin by an automated algorithm, but results can vary between populations.
- Images with varying burn depths could also be classified using deep learning methods on patients of light skin types

<u>Knowledge gaps:</u>

- It is unknown what are the accuracy levels of automated algorithms which could be developed using images of varying skin types and in “real-life” conditions for the identification of the wound and for the classification of their surgical thickness

Box 4. Automated burn diagnosis (Study IV).

RATIONALE

Whereas burn injuries affect mostly populations in resource-scarce settings, most of the studies related to the referral, triage and transfer of patients to specialised burn centres have been performed in HICs. The high caseload of patients as well as the availability of burn centres make the Western Cape province of South Africa a good site for the evaluation of different tools that may be applied for diagnosis and triage. An assessment of routine triage tools currently in utilisation at admission to burn centres such as referral criteria and mortality prediction scores can be used for resource allocation and quality improvement. The evaluation of current standards would assist in determining whether the resources at specialised burn centres are used for those that would benefit most from this type of care. Digital health tools which have either already been introduced such as remote consultations or which are in development, such as automated diagnosis, need to be appraised before their introduction at point of care. These tools offer the opportunity to overcome borders and distances, and can be useful to treat burn patients worldwide, as technologies are available both in HICs and LMICs. In order to maximise the impact of the small number of specialists at hand, it is necessary to determine whether remote consultations performed by specialists who are less familiar with the patient's settings are accurate. Similarly, it is crucial to evaluate whether an automated algorithm can be developed to diagnose burns of patients from different populations.

AIM AND RESEARCH QUESTIONS

The overarching aim of this thesis is to determine the potential of diagnostic support tools for referral and triage of acute burns injuries. More specifically, sub-aims include the assessment of routine and digital health tools utilised in South Africa and Sweden: referral criteria, mortality prediction scores, image-based remote consultation and automated diagnosis.

Routine triage tools at admission to specialised burn centres (Studies I and II)

Referral criteria (Study I)

- What is the level of adherence to referral criteria upon admission to a paediatric burn centre?
- To what extent are each of these referral criteria associated with the care received?

Mortality prediction scores (Study II)

- What are the determinants associated with in-hospital mortality at admission to an adult burn centre?
- To what extent can the ABSI score be used as a source of triage in this setting?

Image-based digital health tools for remote burns diagnosis (Studies III and IV)

Remote consultation (Study III)

- Are remote assessments of comparable accuracy when made on handheld devices compared to a computer screen?
- How accurate is the image-based remote diagnosis of burns commonly presenting to emergency centres when viewed on a handheld device?

Automated diagnosis (Study IV)

- What is the accuracy of an image-based deep learning algorithm for identifying a burn wound?
- What is the accuracy of an image-based deep learning algorithm for classifying burn depth (in terms of surgical needs)?
- How are those results altered by skin types?

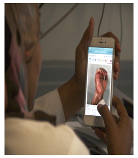
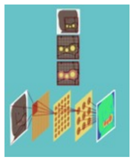
Area of investigation	Study	Tool assessed	Knowledge gaps	Research Questions	Study population		
Routine triage procedures	I	Referral criteria 	Adherence to referral criteria at admission to burn centres in resource-scarce settings has not been evaluated, and the relation between adherence and patient management is unknown	- What is the level of adherence to referral criteria at admission to a paediatric burns centre? - To what extent each of these referral criteria are associated with the care received?	Specialised burn centres	Paediatric	
	II	Mortality prediction scores 	Characteristics associated with mortality remains to be clarified, and whether the existing ABSI score can be used in a resource-scarce setting is unclear	- What are the determinants associated with in-hospital mortality at admission to an adult burn centre? - To what extent can the ABSI score be used as a source of triage in this setting?		Adults	
Image-based digital support	III	Remote Consultation 	Too little information exists on the ability of different groups of burn specialists to accurately diagnose acute burn injuries on handheld devices	- Are remote assessments of comparable accuracy when made on handheld devices compared to a computer screen? - How accurate is the image-based remote diagnosis of burns commonly presenting to emergency centres when viewed on a handheld device?	Point of care	Specialists	
	IV	Automated diagnosis 	Only little research has been performed to develop an automated algorithm for burn injuries diagnosis using images of varying skin types	- What is the accuracy of an image-based deep learning algorithm for identifying a burn wound? - What is the accuracy of an image-based deep learning algorithm for classifying burn depth (in terms of surgical needs)? - How are those results altered by skin types?		Algorithm	

Figure 6. Overview of the studies

MATERIALS AND METHODS

This thesis is based on four studies presented in Figure 6.

Routine triage tools at admission to specialised burn centres (Studies I and II)

Setting

Studies I and II took part in each one of the two specialised burn centres of the Western Cape of South Africa: Study I at the paediatric one (Red Cross War Memorial Children's Hospital; hereafter shortened to Red Cross Hospital), and Study II at the adult one (Tygerberg Hospital). The Western Cape is one of South Africa's nine provinces and is located at the Southwestern tip of the country. It is the third largest province in terms of both land and population, representing 10.6% and 11.8% of the country's land and population respectively [239, 240].

The province is the second largest immigrant-receiving province, with an increase of approximately 470,000 additional immigrants expected in 2021 compared to 2016, and an increase in population size of 20% observed between 2011 and 2020 [240, 241]. The population of the province is furthermore unevenly age-distributed, with 32% of the population being less than 20 years old of which 15% have reported experiencing hunger [240, 242]. About one in five households are not living in formal housing [242], and slightly over 8% of the Western Cape's population did not have access to electricity for lighting in 2018 [239].

The healthcare system in South Africa is two-tiered and divided into a public and a private system producing high inequities in access to healthcare and health outcomes [243]. It was estimated that 16% of South Africans used the private healthcare system while the remaining 84% were users of the publicly funded system [244]. Still, those using the private system consumed over 50% of healthcare expenditure in the country, and were taken care of by about 80% of the country's medical specialists [243]. A National Health Insurance financing system was approved by the South African Government in 2017 with the aim to "*provide quality affordable health services to all South Africans based on their needs*"[245]. A recent report however concludes that these political strategies aiming to reduce health inequality and inequity by 2030 are not yet properly implemented in terms of numbers of health care workers, whether they be nurses, general practitioners or clinical specialists [246]. In the Western Cape, up to three out of four inhabitants are not covered by a medical aid scheme [242].

According to its latest report in 2016, the Western Cape public healthcare system consists of approximately 435 primary healthcare clinics, 34 district hospitals, 5 regional hospitals and 3 tertiary hospitals [247]. With this relatively high number of healthcare facilities, the province has the highest proportion of children living less than 30 minutes away from the closest healthcare facility in the country [242]. However, burn care has to compete with a quadruple burden of disease which includes infectious diseases, maternal and child mortality, non-communicable diseases and violence [248].

As mentioned above, there are two burn centres in the province, which together have 46 beds and manage approximately 1950 cases annually, although the paediatric burn centre manages over three times more cases than its adult counterpart [51]. According to the provincial guidelines minor burn injuries should be treated at primary health centres mostly run by nurses with limited expertise in the field. Intermediate burns should be taken care of at provincial emergency centres in district hospitals while larger burns should be dealt with at level 2 provincial hospitals with surgical infrastructures. Only the most complex burns should be referred and admitted to one of the provincial burn centres (see Figure 7 for definitions of the referral criteria) [93, 159, 248].

REFFERAL CRITERIA FOR TRANSFER TO BURN CENTRES

Age: Less than 2 years or over 60 years.

Severity: Partial thickness burns with TBSA>15% in children or with TBSA >25% in adults; or full thickness burns with TBSA >15% in both children and adults.

Anatomical site: Face, hands, feet, genitalia, perineum, major joints, or circumferential burns. (These burns could also be dealt with at level 1 or 2 but discretion must be used).

Inhalation injury: Requiring ventilation for more than 48 hours.

Mechanism of injury: Exposure to ionizing radiation, high pressure steam, high tension electrical injury, hydrofluoric acid injury >1%, or suspicion of a non-accidental burn injury.

Existing co-morbidity: Cardiac limitation and/or myocardial infarction within 5 years, respiratory limitation of exercise, uncontrolled type 1 diabetes, pregnancy, medically or disease induced immune-suppression for any reason, existing psychiatric or suicidal tendencies, or suspected drug/alcohol abuse.

Severe associated other injuries: For example: polytrauma or crush syndrome.

Figure 7. Western Cape provincial referral criteria for transfer to one of the two specialised burn centres [93].

Data collection procedure

Patients admitted at the burn centres were identified from the centres' admission books and their hand-written medical files were then retrieved from the archive services at the respective hospitals. Standardized electronic case report forms were created and used to collect data (see Appendix 1 for data collection at Red Cross Hospital and Appendix 2 for data collection at Tygerberg Hospital). The forms captured data on the patient, the injury, referral, management and outcome. Patient information collected included age, gender, and previous medical history. Injury information collected included injury mechanism, burn severity (depth), size (expressed as percentage TBSA), and anatomical site involved. Referral information retrieved included mode of transport to the hospital, referring hospital, and adherence to each of the provincial referral criteria (see Figure 7). Finally, patient management and outcome were recorded in terms of admission to the intensive care units (ICU), treatment, surgery procedures, length of stay and mortality. For Study II at the adults' burn centre, the ABSI score was recorded, either by including the one specified by the doctors in the patient's file or by calculating it based on available information.

Samples

a) Inclusion and exclusion

Referral criteria (Study I)

Data were collected at Red Cross Hospital's burn centre for five consecutive winters (when patient load is at its peak; May 1st- August 15th) from 2011 to 2015 as the centre was modernised and upgraded in 2011 to provide better care conditions and improve patient outcome. All paediatric patients (less than 13 years old) admitted to the centre for acute burns during the study period were eligible for inclusion. Exclusion criteria constituted missing or incomplete files, septic cases, those readmitted, those admitted after several visits to the outpatient clinic, and patients who were not treated for burns.

Mortality prediction scores (Study II)

The study included all patients admitted to the Tygerberg Hospital's burn centre for a burn injury during the period from January 1st 2015 to December 31st 2016. Exclusion criteria covered missing or incomplete file records. Furthermore, patients who had no record of admission within their medical files, those who were readmitted, those who were admitted solely for palliative care, and those with a delayed (>1 week) admission were excluded. For mortality analyses, only flame burns patients were included due to the high proportion (96%) of fatalities being from that mechanism.

b) Description of the cases

A total of 1165 paediatric and 372 adult patients were included in Study I and II respectively. Figure 8 presents the age and gender distribution of the patients included in the two studies, while Table 1 presents the injury characteristics of the cases included in each study.

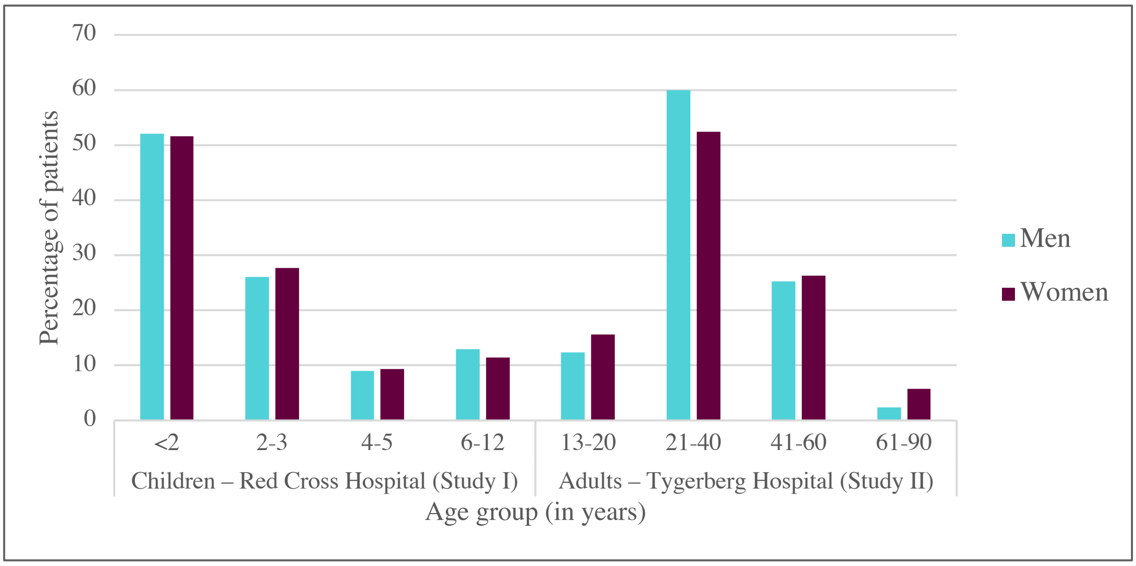


Figure 8. Distribution of patients by gender and age group included in studies I (n=1165) and II (n=372).

Table 1. Injury characteristics of cases included in each of the burn centres, in Study I for paediatric cases at the Red Cross Hospital (n=1165) and in Study II for adult cases at Tygerberg Hospital (n=372)

	Paediatric		Adults	
Injury Characteristics	n	%	n	%
Mechanism				
Hot liquid	953	81.8	72	19.4
Hot object	78	6.7	5	1.3
Fire/Flame	108	9.3	263	70.7
Electrical or Chemical	23	2.0	28	7.5
Unknown	3	0.3	4	1.1
Anatomical site[a]				
Head, face and neck	594	51.0	259	69.6
Arms and/or hands	714	61.3	319	85.8
Trunk	605	51.9	250	67.2
Genitalia/Perineum	112	9.6	31	8.3
Legs and/or feet	446	38.3	183	49.2
Burn size (TBSA, in %)				
≤5	473	40.6	42	11.3
6-10	372	31.9	52	14.0
11-15	183	15.7	42	11.3
16-30	107	9.2	122	32.8
31-50	20	1.7	73	19.6
>50	1	0.1	41	11.0
Unknown	9	0.8	0	0.0
Burn depth[b]				
Superficial-partial	1021	87.6	24	6.5
Mid-partial/Indeterminate	15	1.3	106	28.5
Deep-partial	N/A	N/A	53	14.3
Full	102	8.8	152	40.9
Unknown	27	2.3	37	10.0
Inhalation injury				
No	1132	97.2	197	53.0
Yes	33	2.8	175	47.0
Intent				
Unintentional	1139	97.8	274	73.7
Intentional	22	1.9	94	25.3
Unknown	4	0.3	4	1.1

[a] Data not mutually exclusive; [b] At the paediatric burn centre burn depth was recorded according to the following three categories: partial, indeterminate and full thickness. N/A: not applicable

Regarding outcome, 38.0% of the paediatric cases underwent surgery during their stay versus 71.0% for the adult ones. Furthermore, length of stay was much longer at the adult burn centre with 80.9% of the patients staying longer than a week, but only 25.7% of the patients stayed that long at the paediatric burn centre. Finally, with regards to mortality, 20.8% of the patients admitted to the adult burn centre died due to their injury, a number even higher among flame burn patients (27.8%) while none of the paediatric cases included in Study I died during their stay.

Data analyses

Referral criteria (Study I)
Adherence to each of the seven referral criteria as well as adherence to the referral criteria list as a whole was measured by: $\frac{\text{(cases with at least one criterion identified)}}{\text{(total number of cases)}} \times 100\%$ and was expressed together with 95% confidence intervals (CIs).

Further analyses were performed to assess whether any of the individual referral criterion was associated with the patient's care at the burn centre. In this case intensive patient care was defined as: requiring surgery or a hospital length of stay longer than seven days (=1, staying shorter than seven days and not requiring surgery=0). Simple logistic regressions were conducted with patient care as an outcome, and the individual referral criteria (fulfilled=1, not fulfilled=0) as exposure variables and expressed as Odds Ratios (ORs) with 95% CIs. Those analyses were stratified by the patient age in two groups, those <2 years and those ≥2 years.

Mortality prediction scores (Study II)
Associations between in-hospital mortality and patient, injury and admission-related characteristics were assessed using univariate logistic regressions. In-hospital mortality (yes=1, no=0) was regressed individually on gender (woman=1, man=0), age (categorical), depth (categorical), size (TBSA, continuous), inhalation injury (yes=1, no=0), comorbidity (yes=1, no=0), intent (intentional=1, unintentional=0), time to admissions (2-7 days=1, 0-1 day=0), referral status (not referred=1, referred=0) and level of referring hospital (hospital=1, clinic=0). Odds ratios with 95% CIs are reported. Using the same outcome variable (mortality), multivariate logistic regressions were performed with all exposure variables which were significantly associated with mortality in the univariate models. Statistical significance was defined as a p-value<0.05.

Assessment of the ABSI score was performed through a comparison between the mortality previously described [181] and those observed at the centre for each score. Sensitivity and specificity were thereafter measured in our sample using an ABSI score of 8 as a cut-off which should represent a 50% mortality risk.

Image-based digital health tools for remote diagnosis (Studies III and IV)

Overall image data collection

A database of images of acute burn injuries was constructed consisting of images collected from two data sources: one dataset in South Africa and one in Sweden. Image collection in South Africa was initialized together with the implementation of an mHealth App for acute burns diagnosis (initially moBurnZA [207], then Vula, vulamobile.com). Collection of the images were part of the evaluation of the implementation procedure. Patients admitted at one of the two burn centres in the Western Cape and at the Edendale hospital's burn centre in Pietermaritzburg, Kwa-Zulu Natal from 2015 to 2018 were requested to participate and gave consent. Patients who were referred through the Vula app to one of those centres were also included. Pictures were taken solely with a smartphone available on site, or directly through the Vula app for remote cases. All pictures were taken in “real-life” settings and therefore had varying quality, background, lighting, and distance from the wound.

In Sweden all images were collected from admitted patients at the burn centre of Uppsala University Hospital from 2006 to 2019. Pictures were captured during the patient’s stay to follow-up wound closure as part of standard care. The images were captured using the centre’s own best performing camera at time of capture, whether it was using a standard digital camera or later a smartphone’s camera. Images were all captured in the patient’s hospital room or operation room, with similar lighting and background

Together with the images, deidentified data related to the patient’s age group and gender as well as injury information related to the burn depth, burn size, body part involved, and burn mechanism were all included when available.

Remote consultation

The third study was questionnaire-based and involved 26 participants who were asked to give a diagnosis using their handheld device (smartphone or tablet) on 51 burn images representing typical cases seen at emergency centres in the Western Cape province.

a) Selection of images

Based on data previously collected in eight emergency departments in the province [249], ten (five adult and five paediatric) typical cases were chosen according to those most commonly presenting at those health centres. A selection of 5-10 images was made from the above South African database to represent each of the defined typical cases as well as to include a variety of injury parameters such as size, depth or burn mechanism. Each image represented only one body part, but one patient could be represented in several cases if there were several body parts involved. Those images were then presented to an emergency medicine specialist who confirmed the representativeness and appropriateness of the selected images. Based on his comments, a smaller final selection of five or six images per typical case was made, resulting in a total of 51 images to be included in the survey.

b) Data collection tool

A web-based survey was built on the online platform SurveyMonkey (Appendix 3). It started with general questions related to the participant’s background, their experience with both burns care and remote consultation, as well as the type of device used (smartphone or tablet). The 51 images were then presented together with a basic case description including patient’s age, gender and burn mechanism. The participants were requested to assess the burn’s size (expressed as percentage TBSA), and to select the burn’s depth (out of four options from superficial-partial to full thickness). The images were presented in a random order for each participant to reduce fatigue bias. Before ending the questionnaire, the participants were requested to rate whether they felt comfortable giving a diagnosis on a handheld device and whether images were useful in making the diagnosis.

c) Study participants

Twenty-six participants with expertise in burn diagnosis either from training or from clinical experience were purposively selected from three groups: 1) physicians practicing as tele-experts in the local burn mHealth project (Vula; [207]), 2) burn specialists from other South African provinces who were in the professional network of participants from the first group, 3) Swedish burn specialists who were involved in related studies. These participants were subsequently divided into the following three groups: 1) South African emergency medicine (EM) specialists (n=11), 2) South African burn specialists (n=8), and 3) Swedish burn specialists (n=7). All participants were contacted by email which included a link to the web-survey that had to be filled in on the participant's handheld device. Participants could pause the survey and continue filling it at a latter occasion.

Eight of the participants were asked to fulfil the survey a second time on a laptop computer, at least two weeks later. The computer, with fixed settings, was provided by the research team, an appointment was therefore planned with each of the participants at a time and place of their convenience.

d) Statistical analyses

Diagnostic accuracy for assessments performed both on handheld devices and on the computer were compared to bedside clinical assessment which was used as a gold standard. It was measured using a two-way mixed effect intraclass correlation coefficient (ICC) for burn size and burn depth where it was used as an equivalent for weighted kappa coefficient. ICC was also used to measure inter-rater reliability between all participants, and intra-rater reliability for participants who performed the survey both on a handheld device and on the computer. Analyses were performed for all cases combined as well as stratified by case group: paediatric and adult. The interpretation of the ICC followed the recommendations by de Vet [250] whereby ICC scores lower than 0.70 signified low correlation, scores between 0.70 and 0.80 signified acceptable correlation, and scores higher than 0.80 signified high correlation. For burn depth, sensitivity and specificity was also measured after dichotomizing the results based on the need for surgery (superficial-partial and mid-partial thickness versus deep-partial and full thickness).

Automated burn segmentation and surgery classification

The fourth study involved the training and assessment of two image-based deep-learning algorithms to first identify and segment burn injuries and secondly to classify the surgical need for each burn.

a) Selection of images

A total of 1105 images were included in this study after being selected from the database presented above. In order to be included, images had to present cleaned and scrubbed burn wounds which were photographed within 48 hours post injury. The database consisted of 35% of images (n=391) collected in Sweden in whom patients have lighter Fitzpatrick skin types (1-3) and 65% of images (n=714) collected in South Africa in whom patients have darker skin types (Fitzpatrick 4-6) [251]. The 1105 images were obtained from 387 patients of which 51% were children.

To adjust for body parts respective sizes, images were individually scaled according to available anthropomorphic measurements [252-254]. Using either an image annotation software (ImageJ [255]) or directly on the algorithm training platform Aiforia Create, images were then individually and manually annotated by trained nurses and medical students familiar with burn injuries to segment the wound from normal skin or background on a pixel-by-pixel basis using a binary mask. Classification of the need for surgery was made on an image-level based on the burns expert's depth diagnosis.

A total of 536 background images were also added to the training of the wound identifier algorithm in order to improve the segmentation of the burn wound compared to healthy skin and background objects such as clothes, bed sheets or medical instruments. These were obtained from two publicly available online datasets [256, 257].

a) Training of the deep learning algorithms

Two deep CNNs were trained separately using a commercially available platform for medical image-based deep-learning analyses Aiforia Create. The first algorithm identifies and segments the burn wounds from everything else in the image. The second algorithm classifies each image based on their depth into one of two categories: surgical burns which require surgical intervention for example for skin grafting because they are of deep-partial or full thickness; and non-surgical wounds which are superficial- or mid-partial thickness burns and are manageable with conservative treatment possibly at lower level of care.

Figure 9 presents the splitting of the images into training, testing and validation sets. The images were split into two with 70% of the images forming a training set, and the other 30% of the images forming an independent validation set. Proportion of images based on skin types and surgical classification was maintained in both sets.

The training for the wound identifier algorithm included 773 burns images and the 536 background images. The training area included the whole image and the area to be segmented was the burn area. For the background images, again the training area was the whole image, but these images did not have any annotations. Those background images were not used for the second algorithm related to surgery classification. In the latter, only the wound areas themselves were used as the training areas, and they were separated into two categories based on the burns experts' diagnosis of burn depth either surgical or non-surgical.

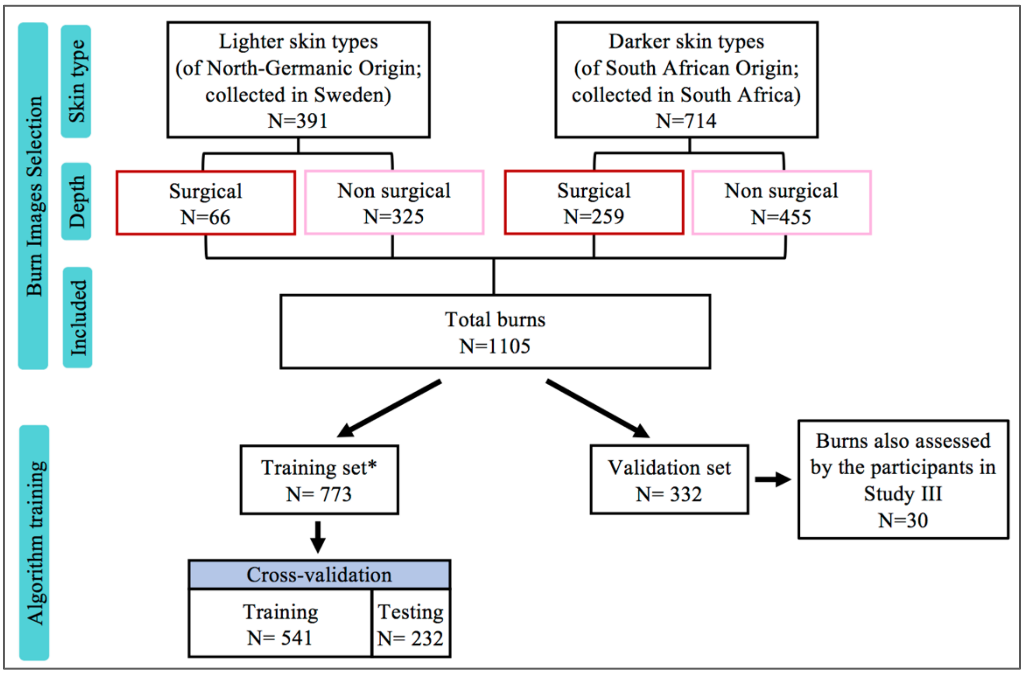


Figure 9. Consort diagram of included images in each of the algorithms.
* In the wound identifier algorithm, 536 background images were also added.

For both algorithms the training set was then subdivided for a three-fold cross-validation into a random 30% testing set, and the remaining 70% were used for training (representing 916 images in the first algorithm and 541 images in the second algorithm). After the verification that all three trainings obtained similar results, a final training was performed using the same settings and 100% of the training set prior to be exported and evaluated on the validation set. Furthermore, in order to assess the algorithms' performances across skin types, separate trainings using 100% of the images with each skin types were performed.

For all algorithms a maximum of 30,000 iterations was used for training, or until the algorithm did not make any progress after 750 consecutive iterations. Feature size was predefined at 125 units for the wound detection algorithm, and 190 units for the surgery classification algorithm. The following image augmentation settings were used for all algorithms: variation in scale (± 10%), aspect ratio (± 10%), shear distortion (± 10%), luminance (± 10%), contrast (± 10%), white balance (± 10%) and variation in image compression quality (40–60%).

b) Statistical analyses

Segmentation results of the first algorithm for wound identification was measured on a pixel level for each image and then aggregated across respective image sets (for the training and validation sets and by skin types). Sensitivity (percentage of pixels identified as burn areas out of the whole burn area), precision (or positive predictive value; percentage of pixels of burnt area out of all those identified as a burn by the algorithm), and F1 score (or dice coefficient; the harmonic mean of the sensitivity and the precision) were measured. Comparisons in the algorithms' performances by skin type was assessed using a non-parametric Mann-Whitney U-test.

For the surgery classification algorithm, while the outcome was binary (surgical burns of deep-partial or full thickness and non-surgical burns of superficial- and mid-partial thickness) the algorithm defined for each image an area in pixels that would require surgery or not. The Receiver Operating Characteristic (ROC) curve as well as the area under the ROC curve (AUC) were measured using an online software [258]. An image was then classified as a surgical burn when >1% of the wound's pixels were identified as such. The success rate was the number of images correctly classified over the total number of images in a given set. Sensitivity represents the percentage of images which had >1% of pixels identified as surgical burn out of all images that required surgery. Specificity was measured as the number of images which had <1% of identified surgical burn pixels out of all images that did not require surgery. Sensitivity and specificity are presented with 95% CIs. This was measured for the validation set overall and for the two validation sets stratified by patient skin type.

Ethical considerations

The treatment of acute burns in LMICs inevitably comes with a number of ethical considerations, first and foremost with regards to the principle of justice and access to care. Studies I and II related to the triage of patients and therefore a selection. In settings like South Africa where all patients cannot be cared for with the resources available, treatment decisions need to be made by the physicians [139, 163, 165]. This usually comes with the use of a utilitarian approach where the well-being of the majority is prioritised, meaning well-being might be denied for others. While providing justice for all patients should be ultimately aimed for, it is deemed unreasonable to use many resources for a patient who may likely not survive. The use of triage scores such as the one evaluated in Study II is linked with dilemmas in patient care. Futility cut-offs are useful for avoiding unnecessary transfers, yet using lower thresholds could lead to accepting lower standards of care for patients in resource-scarce settings [187]. Therefore, the improvement in the level of quality care for all in LMICs should be the goal and carefully selected futility cut-off should be used to avoid unnecessary transfers rather than as expected mortality goals [139, 166]. On the other hand, Study III and ultimately Study IV aim to reduce inequities by providing specialists advice for all patients, even those at a distance and in turn increase the principle of justice for all.

Development of image-based remote diagnosis, whether it is through consultation by specialists (like in Study III) or by an automated algorithm (like in Study IV), are related to a number of ethical issues. These include respect of patient autonomy and also the awareness of such systems by all stakeholders [259]. In addition, safety is of paramount importance when introducing new methodologies and must be assessed using in depth evaluations. The use of digital health solutions should not be an excuse for substandard ethical care [260].

Several other ethical considerations to be reflected upon include the use of retrospective data collection of patient information in studies I and II as this required safeguarding sensitive information. For that purpose, all data were anonymised prior to analyses and results were reported in an aggregated manner.

Study III deals with the concern of voluntary participation of specialists and anonymity. An online questionnaire methodology was used to ensure anonymity and all participants were made aware prior to participation that their participation was voluntary and would not affect their work, nor their position. They were also assured that no judgment of their clinical ability would be performed.

Study IV is at the proof-of-principal stage and does not involve additional ethical issues such as the responsibility of the diagnosis or the continuous evaluation and improvement of the system. Yet these will need to be addressed in the long-term.

All data were available only to the research team and saved on password-protected files. Ethical approvals were obtained from the University of Cape Town (South Africa) Health Research Ethics Committee (452/2015), the Stellenbosch University Health Research Ethics Committee (N16/10/125, N16/09/107, N13/02/24), the University of Kwa-Zulu Natal Ethics Committee (BCA 106/14) and the Uppsala Ethics Committee (Dnr 2016/279).

RESULTS

Routine triage tools at admission to specialised burn centres (Studies I and II)

Referral criteria (Study I)

What is the level of adherence to referral criteria at admission to a paediatric burn centre?

Adherence to each of the referral criteria is presented in Table 2. Overall, 94.8% of the patients admitted to the two burn centres in the Western Cape (the paediatric one at Red Cross Hospital and the adult one at Tygerberg Hospital) were admitted in adherence with the local referral criteria. While 6.6% of the paediatric patients were admitted without adhering to any of the referral criteria, less than one percent of admitted adult cases did not fulfil any criteria. These figures remained stable over the years, both in the paediatric population (z=0.13, p-value =0.897), and in the adult's centre. On average, 1.7 criteria could be identified in those paediatric cases that fulfilled at least one criterion whereas 2.5 criteria could be identified on average in adult cases. The criterion for anatomical site was the one most often fulfilled in both child and adult cases. Among paediatric cases, the criterion for age (<2 years) was also fulfilled by over half of the patients. This criterion for age (considering patients >60 years) was on the other hand only fulfilled by 3.5% of the adult cases. All other criteria were fulfilled at a much greater extent in the adult patient group.

Table 2. Level of adherence to each referral criterion for patients presenting at each of the burn centres, at Red Cross Hospital for paediatric cases (n=1165) and at Tygerberg Hospital for adult cases (n=372)

	Paediatric		Adult	
Criteria	n	%	n	%
Overall adherence	1088	93.4	369	99.2
Anatomical site	992	85.2	349	93.8
Age	604	51.9	13	3.5
Severity	129	11.1	185	49.7
Inhalation injury	33	2.8	160	43.0
Existing co-morbidity	35	3.0	104	28.0
Mechanism of injury	45	3.9	96	25.8
Severe associated other injuries	0	0.0	24	6.5

To what extent are each of these referral criteria associated with the care received?

At the paediatric burn centre – where the majority of the patients had less severe burns than in the adult burn centre – a composite outcome for intensive patient care was built that measured both the need for surgery and a long length of stay (> 7 days). Results of the logistic regressions between referral criteria and intensive patient care are represented in Figure 10. Adherence to the list of referral criteria as a whole was not associated with the care received when including all patients (OR=0.96; 95% CI: 0.60-1.54). However, in patients not fulfilling the age criterion (≥2 years), fulfilling at least one other referral criterion was associated with higher odds in intensive patient care (OR=1.76; 95% CI: 1.39-2.23). Specifically, two criteria were individually associated with higher odds of undergoing surgery or staying longer than seven days in this age group (≥ 2 years): the severity criterion and the inhalational injury criterion. In the younger age group, only the criterion related to severity was associated with patient care. Patients fulfilling that criterion had 19.4 higher odds of more intensive care than patients who did not fulfil that criterion.

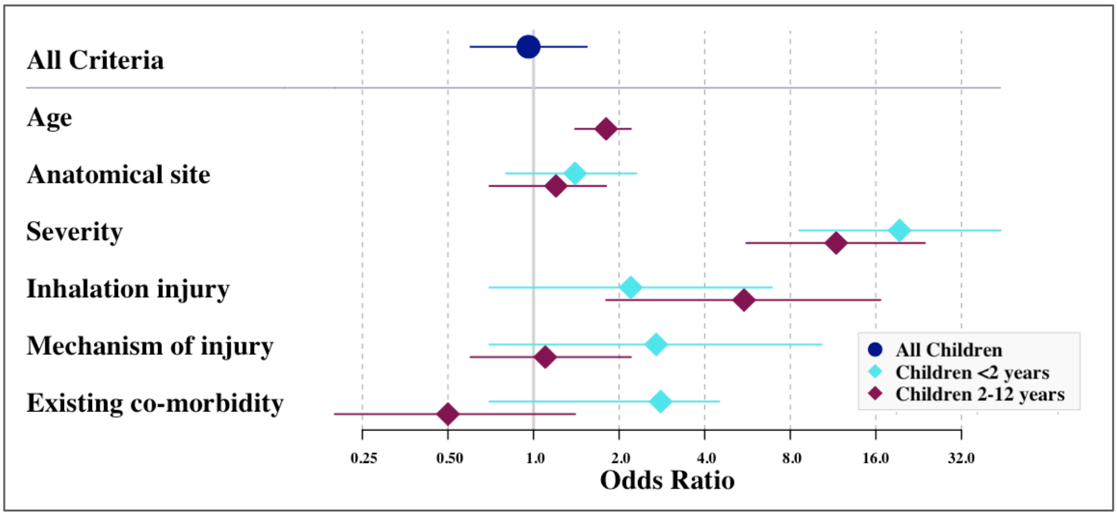


Figure 10. Forestplot of associations between adherence to the referral criteria and intensive patient care. The points represent the odds ratios, and whiskers the 95% CIs. Lack of overlapping an odds ratio of 1.0 represents significance.

Main Results:

- Admissions to the paediatric burn centre were in adherence with the provincial referral criteria
- Referral criteria for anatomical site and age were identified in over half of the paediatric patients admitted
- Three criteria were associated with intensive patient management: age, severity, and, in the older age group, inhalation injury

Box 5. Referral criteria (Study I)

Mortality prediction scores (Study II)

What are the determinants associated with in-hospital mortality at admission to an adult burn centre?

One in five patients who were admitted to the adult burn centre expired during their stay. Of these 76 patients, all but three had sustained flame burns. In flame burn cases, the patient, injury and admission characteristics associated with in-hospital mortality were investigated and results are presented in Table 3. While age was not associated with mortality, gender was. Women had 2.2 higher odds of having a fatal injury than men did. With regards to injury characteristics, patients who had deep partial or full thickness burns had 5.3 higher odds to die of their injury than patients who had superficial- or mid-partial burns. Burn size was also associated with mortality, whereby a 1% increase in TBSA increased the odds of a fatal injury by 1.1. Similarly, inhalation was also a predictor of mortality with 4.3 higher odds for patients with an inhalation injury compared to those with no inhalational components. On the other hand, the presence of comorbidities and the intentional aspect of the injury were not associated with mortality. Regarding admission-related characteristics, time to admission and the level of referring hospital were not associated with mortality, whereas the referral status was. Patients who were not referred and presented directly to the hospital were more likely to have a fatal injury than those who were referred from lower levels of care.

Only three variables remained associated with mortality after adjustments. Women were 3.8 more likely to succumb from their injury while at the hospital than men. Referral status also remained associated with mortality, with 2.8 higher odds of mortality in the group of patients who were not referred compared to those who were referred. Finally, burn size remained a predictor of mortality with 1.1 increased odds of mortality per % increase in mortality.

Table 3. Univariate and multivariate associations between patient, injury and admission-related characteristics with in-hospital mortality for flame burn patients admitted at Tygerberg Hospital burns centre in 2015 and 2016 (n=263)

	Mortality		**Crude**		**Adjusted**	
	n	%	Odds Ratios	95% CI	Odds Ratios	95% CI
Patient characteristics						
Gender						
Male (n=175)	39	22.3	Ref		Ref	
Female (n=88)	34	38.6	2.2	1.3-3.8	3.77	1.7-8.5
Age (in years)						
12-20 (n=39)	11	28.2	Ref		Not included	
21-40 (n=146)	35	24.0	0.8	0.4-1.8		
41-60 (n=67)	22	32.8	1.2	0.5-2.8		
61-90 (n=11)	5	45.5	2.1	0.5-8.4		
Injury characteristics						
Burn depth						
Superficial or Mid Partial (n=73)	7	9.6	Ref		Ref	
Deep Partial or Full thickness (n=164)	59	36.0	5.3	2.3-12.3	1.6	0.6-4.2
No information (n=26)	7	26.9	3.5	1.1-11.2	1.8	0.4-7.7
Burn size						
By percentage increase TBSA (n=263)	73	27.7	1.1	1.07-1.13	1.11	1.08-1.14
Inhalational injury						
No (n=99)	12	12.1	Ref		Ref	
Yes (n=164)	61	37.2	4.3	2.2-8.5	1.2	0.5-3.1
Comorbidity						
No (n=185)	47	25.4	Ref		Not included	
Yes (n=78)	26	33.3	1.5	0.8-2.6		
Injury intent						
Unintentional (n=212)	54	25.5	Ref		Not included	
Intentional (n=49)	18	36.7	1.7	0.9-3.3		
Admission-related characteristics						
Referral status						
Referred (n=223)	53	23.8	Ref		Ref	
Not referred (n=40)	20	50.0	3.2	1.6-6.4	2.8	1.1-7.4
Time to admission (in days)						
2-7 (n=72)	17	23.6	Ref		Not included	
0-1 (n=191)	56	29.3	1.3	0.7-2.5		
Level of referring hospital						
Clinic (n=48)	13	27.1	Ref		Not included	
Hospital (n=175)	40	22.9	0.8	0.4-1.7		

To what extent can the ABSI score be used as a source of triage in this setting?

The results of the comparison between initial expected mortality probability using the ABSI score and the mortality observed at the centre are presented in Table 4. The mean ABSI score observed when considering all patients at admission to the burn centre was six, and the highest score observed in patients who did not sustain a flame burn was nine. Within the patients who sustained flame burns, the average ABSI score was seven and the scores ranged from two to thirteen. For each ABSI score, the mortality observed was in the expected range. However, the mortality observed in patients who were in the highest risk group – with an ABSI score of 12 or 13 – was of 100%, with none of the patients surviving their injury. A sensitivity of 84% (95% CI: 76%-92%) and a specificity of 86% (95% CI: 82%-90%) was identified for the ABSI score using as a cut-off an ABSI score of 8. The AUC was of 0.917. When considering only flame burns, the sensitivity increased to 85% (95% CI: 77%-93%), but the specificity decreased slightly to 81% (95% CI: 75%-86%). The respective AUC was of 0.898.

Table 4. Total ABSI score, probability of mortality previously described in [181]; and numbers of patients and mortality (in percent) observed in 2015 and 2016 at Tygerberg Hospital burn centre.

Total ABSI score	Estimated probability of mortality (%)	All patients (n=372)			Patients with flame burns (n=263)		
		Admitted	Mortality observed		Admitted	Mortality observed	
		n	n	%	n	n	%
2-3	<1	44	0	0	21	0	0
4-5	2	104	2	1.9	55	1	1.8
6-7	10-20	119	10	8.4	88	10	11.4
8-9	30-50	59	27	45.8	53	25	47.2
10-11	60-80	33	24	72.7	33	24	72.7
12-13	>90	13	13	100.0	13	13	100.0

<u>Main Results:</u>

- Almost all patients admitted to the adult burn centre fulfilled the referral criteria
- The mortality rate at the centre was of 20%, and this affected almost exclusively patients who had sustained flame burns
- Gender, referral status and burn size were the three characteristics which remained significantly associated with mortality after adjustments for the other variables
- The mortality rate observed was in line with the prediction estimated by the ABSI score although none of the patients in the highest risk group survived

Box 6. Mortality prediction scores (Study II)

Image-based digital health tools for remote diagnosis (Studies III and IV)

Remote consultation by burn specialists (Study III)

Are remote assessments of comparable accuracy when made on handheld devices compared to a computer screen?

The accuracy of burn size and burn depth diagnoses made by eight participants on both a computer screen and on a handheld device are presented in Table 5. Regarding burn size, all assessments performed on the computer were rated as in high agreement with the gold standard (bedside diagnosis) with ICCs ranging from 0.82 for adult cases to 0.90 for paediatric cases. These assessments were also similar to the ones performed using a handheld device by the same participants, as indicated by the high intra-rater reliability across all cases. On the other hand, the assessments of depth had low accuracy, with ICCs ranging from 0.46 to 0.50. The intra-rater reliability measure was slightly higher but still in low agreement.

Table 5. Diagnostic accuracy and intra-rater reliability (handheld versus computer) of size and depth assessments made on computer

Measure	Cases	Accuracy ICC (95% CI)	Intra-rater reliability ICC (95% CI)
Size	Overall	0.85 (0.82-0.88)	0.88 (0.85-0.90)
	Paediatric	0.90 (0.87-0.92)	0.85 (0.80-0.88)
	Adults	0.82 (0.77-0.86)	0.87 (0.84-0.90)
Depth	Overall	0.48 (0.41-0.55)	0.63 (0.57-0.69)
	Paediatric	0.50 (0.39-0.60)	0.65 (0.56-0.72)
	Adults	0.46 (0.35-0.56)	0.62 (0.52-0.69)

How accurate is the image-based remote diagnosis of burns commonly presenting to emergency centres when viewed on a handheld device?

The results of the accuracy of the assessments made by all 26 participants using their handheld devices are presented for both burn size and depth in Table 6. The accuracy of the burn size assessments across all participants was high for adult cases (ICC= 0.81), paediatric cases (ICC=0.81) and overall (ICC = 0.82). Although still considered of high accuracy, the assessments performed by emergency specialists were slightly less accurate than those made by burn specialists from both South Africa and Sweden.

Burn depth assessments of paediatric cases were slightly more accurate than those of adult cases (ICC: 0.61 versus 0.46) but they remained of low accuracy overall. Like for burn size, South African burn specialists performed better than emergency medicine specialists in paediatric cases, but no difference in accuracy performance was observed between groups of participants in the adult cases.

Table 6. Diagnostic accuracy of size and depth assessments made on handheld devices by case and participant group

	Participants		Accuracy	
			Size[a]	Depth[b]
Cases	Country	Specialty	ICC (95% CI)	ICC (95% CI)
Overall	All participants		0.82 (0.81-0.84)	0.53 (0.49-0.57)
	Sweden	Burn specialists	0.87 (0.84-0.89)	0.51 (0.43-0.59)
	South Africa	Burn specialists	0.87 (0.85-0.89)	0.64 (0.58-0.69)
	South Africa	EM specialists	0.80 (0.77-0.83)	0.49 (0.43-0.55)
Paediatric	All participants		0.81 (0.78-0.83)	0.61 (0.55-0.65)
	Sweden	Burn specialists	0.83 (0.78-0.87)	0.59 (0.48-0.68)
	South Africa	Burn specialists	0.90 (0.87-0.92)	0.75 (0.68-0.80)
	South Africa	EM specialists	0.77 (0.72-0.81)	0.54 (0.45-0.62)
Adults	All participants		0.81 (0.78-0.84)	0.46 (0.40-0.52)
	Sweden	Burn specialists	0.87 (0.83-0.90)	0.45 (0.33-0.56)
	South Africa	Burn specialists	0.85 (0.81-0.89)	0.54 (0.43-0.63)
	South Africa	EM specialists	0.79 (0.75-0.83)	0.44 (0.35-0.53)

[a]6 missing values, analysis performed on 1320 cases; [b]27 missing values, analysis performed on 1299 cases

The sensitivity of the need for surgery (superficial- and mid-partial thickness burns versus deep partial and full thickness burns) of the assessments performed on the handheld devices was 75.6% while the specificity was 70.4%.

Main Results:

- The image-based assessments of both burn size and burn depth were of similar levels of accuracy when performed on a computer screen or on a handheld device.
- Accuracy of the assessments of burn size was high across all participant and case groups.
- Assessments of burn depth was of lower accuracy, although South African burn specialists performed better than their emergency medicine specialists counterpart.

Box 7. Diagnostic accuracy of image-based remote consultation (Study III)

Automated burn segmentation and surgery classification (Study IV)

What is the level of accuracy achieved by an image-based deep learning algorithm for identifying a burn wound?

Across all three cross-validation training and testing sets, the sensitivity of the burn identification algorithm was 92.5% (95% CI: 91.9%-93.1%) and 85.1% (95% CI: 83.7%-86.5%). In the final training set using 100% of the training material, the sensitivity of the algorithm was 93.2% (95% CI: 92.4%-94.0%), and the F1 score was 90.2% (95% CI: 89.4%-91.0%). In the two trainings stratified by skin types, the sensitivity was 92.2% (95% CI: 90.9-93.9) and 93.4% (95% CI: 92.4-94.4) in lighter and darker skin types respectively.

Results of the identification algorithm for the validation set as a whole and by skin types are presented in Table 7.

Table 7. Average sensitivity, precision and F1 score of the burn area identification algorithm in the validation set overall, and by skin types.

	Images	Sensitivity		Precision		F1 score		Mann-Whitney U-test
	n	%	(95% CI)	%	(95% CI)	%	(95% CI)	*P* value
Complete validation set	332	86.9	84.9-89.0	83.4	81.5-85.2	82.9	80.9;84.9	
Lighter skin (skin types 1-3)	118	78.6	74.0-83.1	81.0	77.4-84.7	76.9	72.9-80.9	0.0001
Darker skin (skin types 4-6)	214	89.3	87.2-91.5	88.1	86.2-89.9	87.8	85.8-89.7	

What is the level of accuracy achieved by an image-based deep learning algorithm for classifying burn wounds based on their depth in terms of surgical needs?

The burn surgical classification algorithm obtained a sensitivity and specificity of 98% and 88% respectively across the three cross-validation trainings. In the testing sets, these values were of 96% and 71% respectively. In the final training that includes the complete image set, the sensitivity was 99.6% and the specificity was of 93.4%. In the training set comprising only of lighter skin types, the sensitivity was of 97.8% and the specificity was of 100%. In the training set comprising only of darker skin types, the sensitivity was of 80.1% and the specificity was of 97.1%. The results of the validation sets, with all images and stratified by skin types are presented in Figure 11. The AUC was largest in the combined dataset with a value of 0.885. The sensitivity was highest for patients with darker skin types whereas the specificity was highest in patients with lighter skin types.
A total of 30 images included in the validation set had previously been assessed by the participants of Study III. The performances of the algorithm was of 71% and 30% for sensitivity and specificity respectively. As a comparison, the performances of the physicians was of 68% and 65% for the same images.

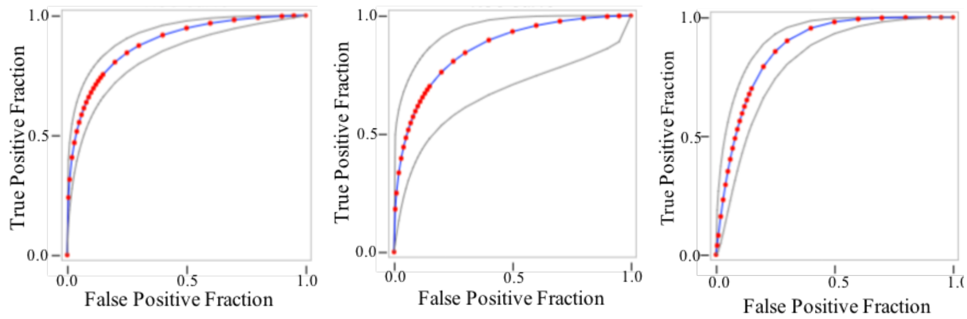
Validation set	All images	Lighter skin	Darker skin
Receiver Operating Curves			
AUC	0.885	0.863	0.875
Success rate % (95% CI)	64.5	78.0	66.8
Sensitivity % (95% CI)	92.5 (87.1-97.8)	75.0 (56.0-94.0)	97.3 (93.5-100.0)
Specificity % (95% CI)	53.6 (47.2-59.9)	78.6 (70.4-86.7)	51.1 (42.8-59.3)

Figure 11. Wound classification algorithm performances results for the complete validation set as well as by skin type

<u>Main Results:</u>

- The algorithm for wound identification could segment burns with relatively high accuracy using images captured in "real-life" settings
- Wound classification according to the need for surgery showed reasonable accuracy with regards to AUC, but dichotomous classification still needs improvements
- While the burn identification algorithm showed better performance for patients with darker skin types, the wound classification had higher accuracy results for patients with lighter skin types

Box 8. Diagnostic accuracy of automated diagnosis (Study IV)

DISCUSSION

Main Findings

Admission to burn centres are in line with existing triage protocols

Observed differences in patient characteristics observed between adult and paediatric patients admitted confirm previous reviews from the African continent [72]. For example, children are most often injured by hot liquids whereas most adults are affected by flame burns. This also relates to the severity of the burns where paediatric patients usually have smaller, and less severe burns; whereas they are larger, deeper and more lethal in the adults population [72]. It also explains the use of distinctive patient outcomes for analyses between the two burn centres. Whereas none of the patients included at the paediatric centre died during their stay, over one fifth did in the adult population. An explanation can also be found in the respective patient managements with the paediatric centre admitting around 68 patients annually per bed when the adults centre admits only 18 patients [51]. In HICs where mortality is also low and where follow-up is more easily available, other outcome measures have been suggested, such as quality of life, psychosocial outcomes or community participation [261].

Overall, adherence to the local referral criteria was high at both the paediatric and adult burn centres. Adherence to these criteria at admission to specialised care vary greatly between burn centres from various contexts [135, 137, 154, 155]. Similar to our results, a few burn centres report high (or even perfect) adherence to the local criteria [135, 154], especially in the adult populations. Results from paediatric burn centres in the United States and Denmark reported much higher rates of over-triage [137, 155]. These differences could be explained by variations in either referral criteria definitions, caseloads, available resources or local cultural practices.

In trauma in general, it is accepted that there could be variations in the definitions of over-triage between HICs and LMICs as referring or district hospitals might not have the sufficient resources to support diagnosis for example using imagery or laboratory techniques or psychosocial help [11]. When looking at admission to burn centres, referral criteria might not be the only factor that comes into play. For example, in an Iranian burn centre only a third of the patients were admitted in adherence with referral criteria, and the majority had been transferred on requests of family members [158]. Similarly, in Australia one third of paediatric patients were admitted for reasons that were other than the severity or location of the burn and which included time at presentation [262].

Results from lower levels of care in the Western Cape have shown that under-referral is high. Once again, this could be explained by other factors. For example, about half of the patients taken care of by pre-hospital emergency services fulfilled at least one referral criterion, but 10% of them refused treatment [121]. Across patients visiting urban clinical health centres and rural district hospitals, 84% of those fulfilling at least one criterion were not transferred to higher levels of care [160]. Even at the trauma unit of Red Cross Hospital, 26% of the patients fulfilling the criteria were not transferred to the burn centre [152]. In this case however, the patients who were least often transferred were those fulfilling the age or site criteria and had generally very small burns [152]. This is also confirmed by the fact that adherence to the referral criteria was not associated with intensive patient care at the burn centre, especially for children under two or those with a burn at critical areas. It also resonates with the results observed in HICs where such patients (with small burns to critical areas) could effectively be treated at lower levels of care or followed as outpatients [263, 264]. This brings up the ongoing discussion that has risen in HICs with the clear distinction of referral criteria definitions between patients who would require burns expertise in the form of outpatient treatment and those who require immediate burn centre referral [91, 142, 156]. However, this type of guidelines might not consider the discomfort of referring clinicians in treating burn patients [265], and the inappropriate treatment and diagnosis reported at point of care [264].

At the adult burn centre, after adjustments for all other variables, mortality was associated with being a woman, having a large burn and being admitted without prior referral. The mortality observed was in line with that seen across the African continent [69], and also very much so like those at a burn centre in the country (in Johannesburg) that admits the same type of caseload (mortality was of 21% overall and 29% for flame burns) [166]. Regarding gender, there are confirming results from other levels of care in the country showing that males have consistently been reported to be more commonly transferred to high levels of care for comparable wound severity [152, 249, 266]. In this thesis a higher number of males were seen at admission to both burn centres. On the other hand, women had higher mortality in the adult burn centre. This corresponds to the findings of the ABSI score whereby gender is one of the prognostic variables [267, 268], but has been debated in other settings [269]. It could be related to differences in physiological characteristics such as hormonal and body mass compositions, as well as to differences in treatment by health care professionals [249, 270, 271].

That the TBSA was associated with mortality is not surprising as it has quite consistently been linked with prognosis for several decades now. On the other hand, that mortality was associated with being admitted without prior referral comes as a bit of a surprise at is was previously shown, in a German burn centre that the earlier the transfer to a burn centre, the better the outcome [157]. An explanation for this difference could be the health system’s organisation with pre-hospital emergency services bringing very severe cases directly to the trauma centre at Tygerberg. Patients who would have likely died prior to transfer and not been reported if they were cared for at lower levels of care were admitted when a bed was available in the burn centre and increased those numbers [159]. Furthermore, early excision and grafting has shown to be a major reason for improved mortality, even in LMICs [272], but there is a lack of burn-specific operative infrastructure in South Africa in general [51], and at Tygerberg Hospital in particular, which could have also explained the high mortality seen in patients admitted directly.

The ABSI score prognostic ability was evaluated at the burn centre as it was occasionally used for patients with the most major burns, in order to verify if it should be adapted to the local patient population and resource utilisation. In Johannesburg, the prognostic model evaluated was the rBaux Score and their results showed – like what was seen at Tygerberg Hospital – that although the prognostic model had to be slightly adapted [166], it was more in line with those of HICs than in another South African burns unit that is not part of a tertiary hospital [187].

Two major issues with both referral criteria and the ABSI score (or any other prognostic model for that matter), is that: 1) clinicians at point of care might not be aware of the existence of the existing protocols [51, 159]; 2) While some of the variables for referral criteria or prognosis evaluation are easily identifiable at point of care, others – which are also paramount – such as accurate diagnosis of burn size and depth are commonly inaccurate at point of care [103, 105, 114, 115].

The development of digital health to improve the communication between levels of care as well as to provide accurate diagnosis could contribute to a better solution.

Image-based digital health provides accurate diagnosis at point of care

Image-based assessments performed on handheld devices (tablets or smartphones) were of similar accuracy as when performed on computer screens. While the American Guidelines for Teleburn suggest the use of a specific high resolution computer screen for the interpretation of burn images, these results support the notion that even handheld devices could be used [23] – especially in LMICs – without providing less accurate standards [259]. These results will comfort practices even in settings where computer are easily accessible in healthcare such as France, as it has previously been reported that transmission of images using smartphones occurred in about half of the cases for evaluation prior to transfer [273].

In order to optimize the use of resources, several voices have been raised to point out whether these criteria should be used as transfer guidelines for major burns or for the identification of injuries that require specialists advice but not acute attention [135, 136, 146, 156, 262]. With that in mind, the American Burns Association has just published a revision of their referral criteria, renamed "*Recommended Guidelines for Transfer and Consultation*" and which are divided into three "*immediate transfer*", "*telemedicine consultation*" and "*outpatient referral*" [142].

Regarding burn size estimation, the assessments performed by all participants were of high accuracy. This confirms prior results of image-based assessments [198, 199, 202] and are promising in demonstrating the potential of remote-consultation for burn size assessments. This could have tremendous implications for patient care and outcome including for referral, triage and diagnosis since size is one of the most significant factors, as shown above. They could also be complemented with alternative suggested methods to assist with the calculation of burns size at point of care, such as with the help of 3D-models [227-229] or with a handheld body scanner [274]. These methods however were all developed in HICs, and should therefore be further investigated in LMICs prior to be implemented.

Concerning burn depth, results were more mixed. They were overall relatively low, although the South African burn specialists performed better than the other two groups, and results for children cases were also better. While burn depth diagnosis can be inaccurate even at bedside [122, 131], some previous results using photographic assessments, were either much less accurate in a study in the Netherlands (ICC=0.28) [198], or slightly better in a Malawian study (κ=0.6)[199].

Regarding the results of the automated diagnosis algorithm, results of the wound identification were of relatively high accuracy with an F1 score of 0.83 which is slightly better than results obtained using deep-learning methods [236, 237]. When looking at the surgery classification, results could be improved, although the overall AUC was of 0.885. A difference could be seen between cases of lighter and darker skin, with very high sensitivity (97%) and low specificity (51%) in the latter whereas both sensitivity and specificity were more in line in cases of lighter skin (75% and 79% respectively). This difference in results between different skin types confirms the results from burn specialists whereby skin characteristics have a consequence on the diagnostic ability [197]. This also echoes to a recent publication where a recent model developed for wound identification between African and Caucasian populations showed lower accuracy in the combined model [235]. Results in the lighter skin type are more similar to what has been previously published and which used similar caseloads and had a success rate of around 80% [275, 276]. These results can also be compared to those obtained using the handheld devices where sensitivity was of 76% and specificity of 70%. The results however tend to go in the opposite direction as what was published previously regarding the photographic assessment of surgery by burn surgeons and referring physicians where sensitivity was high but specificity particularly low (39% for referring physicians) [198].

Methodological considerations

Data collection of patient records

Studies I and II reviewed retrospectively patient individual medical records that were filed in the burn centres for patient medical follow-up during admission. Strengths included the inclusion of almost all patients, and the large amount of data. That there were more patients included in the paediatric hospital mirrors the different patient loads reported between the two centres of the province [51]. Although a systematic process was performed for the data collection with several data collectors, and data verification performed regularly, this type of data collection comes with a number of limitations. First, both the health records and the registers were handwritten, and had to be found in various locations within the burn centres and archives resources. This led to a number of patient files to be unidentifiable, or unreachable despite several attempts. Given the low number of these, there is no reason to believe that there was a systematic bias in the missing files. That being said, it is possible that in the paediatric hospital, no patients were included with associated severe injury, neither were those deceased. This could find an explanation in the fact that they might have been admitted in different departments, or because they were under police investigations and could therefore not be retrieved. The number of deceased patients was however very small, and would have likely not changed the results significantly.

In the identified files, there could have been some missing information as well. To the contrary of other levels of care in the province where large amounts of data have previously been noted [121, 152, 249], most of the relevant variables were complete at the burn centres where patients stay over several days, and where key variables such as age, size or depth are necessary for diagnosis. However, in the adult burn centre, up to 10% of the patients had missing burn depth information. We believe there was no systematic bias in the distribution of those patients, and that information was lacking when visually the depth was obvious to the physician or did not impact on the outcome, for example if a burn was very superficial (good outcome) or a very large burn (bad outcome). Several analyses were performed to identify whether results would be affected by the treatment of this missing data, but they did not. It is also of note that no deep partial thickness burns were identified in the paediatric population. This could be due to the fact that burns were less severe as a whole, but also because depth is not as important for criteria definition within that population (all burns >15% TBSA should be referred) whereas there was a more mixed adults population, that required more often surgery and in which criteria differ between partial thickness burns (TBSA >25%) and full thickness burns (TBSA >15%).

The other limitation associated with the retrospective data collection is that adherence to the referral criteria, as well as the ABSI score were evaluated based on the recorded information. Whether the referral criteria were used for transfer or admission is not known. Finally, the analyses of the data at the burn centre is blind of the patient load at other levels of care. Even if the criteria are fulfilled at arrival, and the over-triage is low, whether this is the case at all levels of care can only be speculated from other studies performed [121, 152, 160] rather than by a prospective follow-up of the same patients. Furthermore, patients who were admitted to the adult burn centre for palliative care were excluded from the analyses, which could have influenced the results. These patients were not treated with the same care or resources as others who underwent curative treatment prior to mortality and therefore even if mortality would have been higher if those were included, the factors associated with this mortality might have been influenced by other decisions. Similarly, evaluation of the ABSI score might not have been representative if those cases had been included.

In both studies only acute burns were included as other burns might present different complications or be admitted for different reasons. Unfortunately, the high pressure on bed availabilities in the South African context might have been a reason for delayed admission. This is even more true when there is a great variation in the resources available between different levels of care, as it has been shown that only 23% of public hospitals in the country had an ICU facility [277].

Use of images

There are a few strengths that should be mentioned with the data collection of the images. First, a large amount of image could be collected from different sources and which had varying background, lightning, sizes, body parts, demographic characteristics or image resolutions. In particular, Study III focused on the inclusion of typical cases presenting at emergency centres in that setting in order to assess whether local physicians, but also those less experienced with that case load could be an alternative solution if the number of local specialists is too small. This is also why a number of uncleaned wounds were included in that study as it has been shown previously that additional tasks for the clinicians at bedside prior to remote consultation might be a reason for low implementation of mHealth tools [208]. On the other hand, in Study IV, patients not only from two different countries were included, but also those presenting at both referring institutions and burn centres were included in order to cover as many possible situations as possible. This is, however, a reason that could have led to the lower accuracy observed, especially in Study IV. Rather than improving the algorithm's performances, the stand was taken to use images that can be of clinical use if implemented. In order to reduce slightly the variation of images, and with, in mind, the guidelines from HICs that suggest wounds should be debrided prior to teleconsultation [23], uncleaned wounds were excluded in Study IV. In the future, education of clinicians at point of care regarding wound cleaning, or the development of algorithms which can also give a diagnosis on an uncleaned wound will therefore be necessary prior to full implementation.

It should also be noted that each image, whether it was for Study III or IV was only attributed on depth, as this is often the case for these types of preliminary diagnosis at point of care when reviewed. There could have been a small number of specific burns that included distinctly several depths, and therefore the thickness most representative in terms of size was always attributed. This could have slightly decreased the accuracy results [199]. Further, the number of images which were of deeper burn depth (of deep partial and full thickness in Study III, and surgical burns for Study IV) was smaller than the other categories, reflecting the caseload. This was especially the case in the lighter skin types. This imbalance could have had an impact on the results [250, 278].

Finally, in practice remote consultation would include additional patient and injury characteristics other than the image submitted for assessment to the participants in Study III. With the use of this additional data (such as burn mechanism, or patient pain), it is likely that the results, especially for burn depth, would have been more accurate. Nowadays, even if the technology uses images as opposed to videos, the turn-around time for image viewing almost immediate, and therefore the communication between practitioners can be considered real-time [19]. Similarly, it is possible to envision to add several variables for the training of the deep learning algorithm in Study IV such as skin type, or once again burn mechanism, in order to improve the obtained results.

Online survey

The participants of Study III were recruited using a purposive sampling method which could have led to sampling bias, and limits the generalisability of the results obtained. Alternative methodology was however not possible given the small number of burn specialists and of emergency physicians who would be susceptible to receive burn cases for evaluation. Whether a larger or different sample of participants would have yield different results is hard to know. Also, participants were invited to use their own devices to complete the survey. All participants did have access to a handheld device, or else we would have provided them with one. This permitted the more realistic situation of which devices were in use at the time in a given context, and also that the participants could fill in the questionnaire at their convenience. In order to reduce response fatigue, participants could pause their questionnaire and resume to it at any later stage. Furthermore, the number of images was carefully selected to permit data analyses while not overburdening the participants which would have limited the sample size. A few missing answers were however identified, and could reflect the most complex cases where a conversation between clinicians might have been useful. Several methods for treating these missing values were investigated, but they did not seem to influence the results. Finally, a relatively long time was permitted for participants who performed the questionnaire twice (on the computer and on the handheld device) in order to reduce recall bias which was unlikely given the high number of images included.

Implications for research, policy and practice

Together these studies provide a snapshot of the current situation at admission to the two burn centres of the Western Cape province in South Africa, as well as demonstrate the potential for digital health tools that are now either established or in initial steps of development. The satisfying results with regards to the high adherence to the referral criteria at admission could contra intuitively reflect the need for an adjustment of these in order to avoid the transfer of patients with small burns. The use of digital technologies, including the mHealth applications now in place could be a reason to modify these criteria in order to better identify which are those relevant for immediate patient transfer and which are recommendations for further evaluation. They could also mention terms such as futility decisions. Since the studies were performed, the Vula App is now part of standard care for referral of patients to the burn centres in the province and could be updated in order to provide even more information to referring clinicians, without burdening the specialists on call.

Most of the tools described in this thesis involve relatively low costs, and could easily be added to current care procedures. Burn care, as an integral part of essential surgery care, suffers from the lack of investments from governments and public health agencies in Sub-Saharan Africa, and in particular in South Africa, where they rather focus on the prevention of malnutrition and infectious diseases such as AIDS (Acquired Immuno-Deficiency Syndrome) [279]. Furthermore, the use of digital health has been suggested as a major way to attain the Sustainable Development Goals in terms of better health [18].

In fact, each of the evaluated methods have the aim to reduce inequity in access to appropriate healthcare. The triage tools provide concrete and objective measures to make a decision regarding referral of patients independent of where the patient is referred from and of their socio-economic status. The digital health tools are even more important in reducing inequities as they have the potential of bringing experts advice to the patients at point of care independently of where the patient is located, what time the patient presents to the healthcare centres, and of any other discriminations. This is even more true for the automated diagnosis, which if properly trained, give an objective interpretation to each case. In a country like South Africa where inequalities are a major burden, any interventions to reduce differences between population groups is particularly beneficial.

The ultimate aim is to provide optimal care for all patients. Until that is not achievable with the available capacity, triage decisions must be taken in order to maximize survival of the greatest number of patients, even if that results in denying treatment for a patient with a poor prognosis [133, 139, 161, 165]. In fact, the care of burn patients in LMICs has been described as similar to that of times of disasters or crisis even in HICs [134, 140]. Results obtained here could be used as a basis for patient care in other acute situations where decisions need to be made rapidly, such as the recent covid-19 pandemic where large numbers of patients require intensive care.

Although most of the thesis focused mostly on the South African context, several of the results could be useful also in HICs, for example in Sweden, where the lower number of cases has led to an over-centralisation of burn care, with large distances and poor burn-specific knowledge at point of care. The use of patients from different backgrounds for the development of the automated diagnosis tool would permit a world-wide application.

Implementation of image-based remote consultation is a reality throughout the world. Yet, automated diagnosis for burns care is still in its early phase, and several additional developments will be needed to achieve sufficient accuracy in order to be used in healthcare. Further research will also be required to investigate the intention-to-use such a tool by clinicians at point of care, and the degree to which burn specialists at burn centres trust the obtained results.

CONCLUSIONS

As a whole the results of the thesis inform on four very different tools that individually assist with the diagnosis, referral and triage of patients with acute burns. At admission to specialised burn centres results obtained from triage protocols such as referral criteria and the ABSI mortality prediction score are in line with expectations. Patients treated at specialised centres are severe cases and besides a few futile cases, are those who would benefit the most from this type of care. An adaptation of the current referral criteria in the Western Cape province of South Africa to assist in differentiating between patients that require immediate transfer from those who require remote consultation from an expert or outpatient care would improve patient care. Similarly, the use of the results from the mortality analyses could assist with difficult cases with regards to futility decisions, and these could be taken prior to transfer of patients to burn centres when the likelihood of mortality is extremely high despite the provision of specialised care. Furthermore, as remote consultation using handheld devices and smartphones is now part of usual care, the results of this thesis demonstrate that assessment of the burn size is accurate using these devices and depth assessment, although not optimal, is also beneficial for improving treatment. In addition, the development of deep-learning based artificial intelligence algorithms enabled the identification of burn injuries and classification of surgical thickness as promising results to assist settings with low access to experts. Further analyses will be required to determine whether these tools can be improved with the addition of an increased number of images or through the implementation of enhanced image capturing methods.

These results are informative with regards to the different solutions needed to reduce health inequities by providing access to specialised centres to those who mostly need it, while treating other patients at point-of-care nevertheless with access to specialist's input, either through remote consultation, or in the future through artificial intelligence. This has public health relevance and applicability both in resource-scarce settings as well as HICs with geographic distances or under high clinical pressure.

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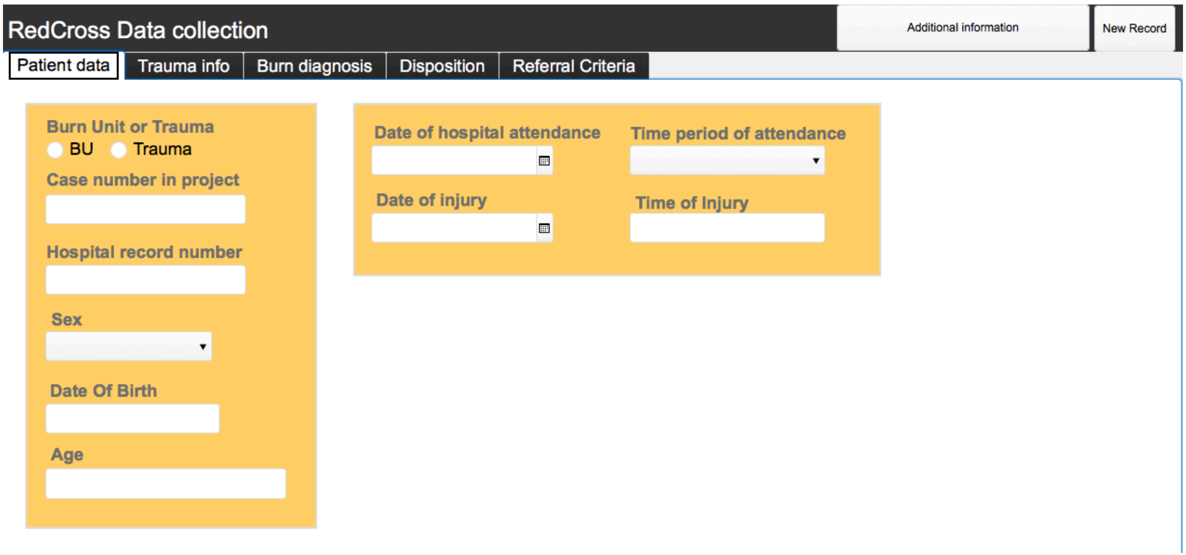
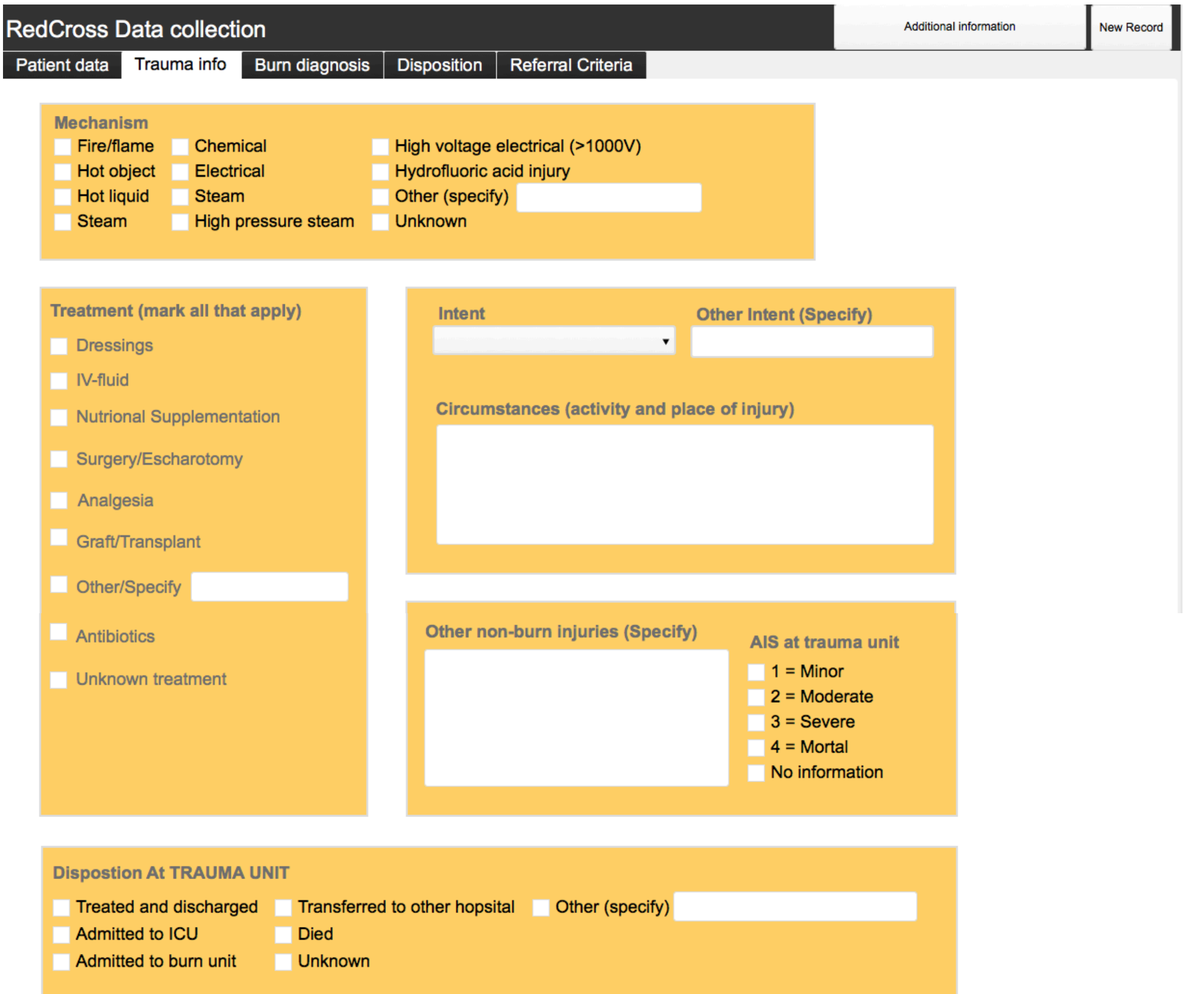
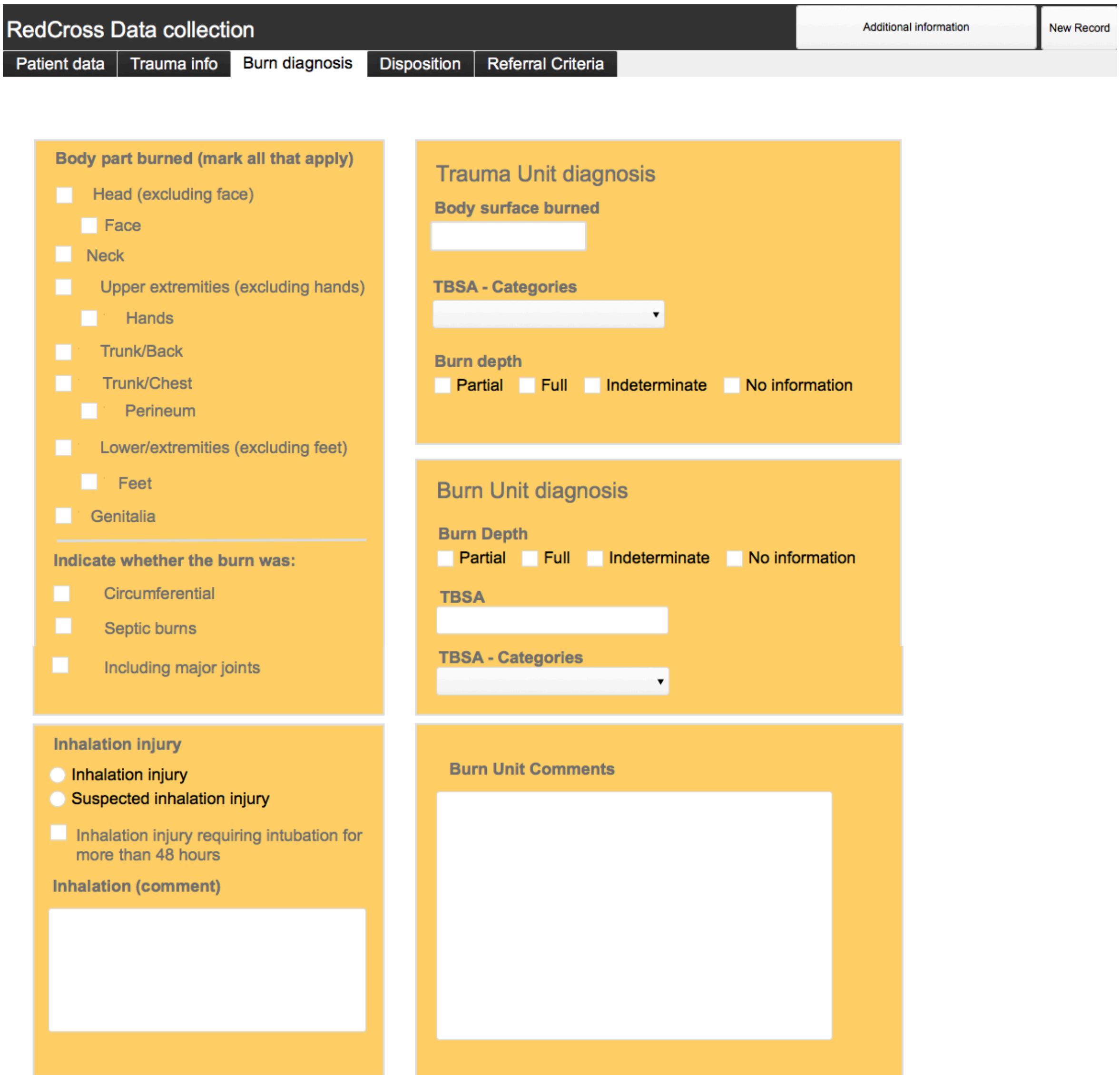
APPENDIX 1. DATA COLLECTION FORM STUDY I







RedCross Data collection

Additional information | New Record

Patient data | Trauma info | Burn diagnosis | Disposition | Referral Criteria

Body part burned (mark all that apply)

- Head (excluding face)
  - Face
- Neck
- Upper extremities (excluding hands)
  - Hands
- Trunk/Back
- Trunk/Chest
  - Perineum
- Lower/extremities (excluding feet)
  - Feet
- Genitalia

Indicate whether the burn was:

- Circumferential
- Septic burns
- Including major joints

Inhalation injury

- Inhalation injury
- Suspected inhalation injury
- Inhalation injury requiring intubation for more than 48 hours

Inhalation (comment)

Trauma Unit diagnosis

Body surface burned

TBSA - Categories

Burn depth

Partial | Full | Indeterminate | No information

Burn Unit diagnosis

Burn Depth

Partial | Full | Indeterminate | No information

TBSA

TBSA - Categories

Burn Unit Comments

RedCross Data collection | Additional information | New Record

Patient data | Trauma info | Burn diagnosis | Disposition | Referral Criteria

SABS Criteria

Criteria	Overrule (met or unmet)
< 1 year old	
1-2 yr old; burns >5% TBSA	
Full thickness burn	
>2 yr old; partial thickness burn >10%	
Burns of special areas - face hands, feet, genitalia, perineum or major joints	
Electrical burns, including lightning	
Inhalation burn resulting from fire or scald	
Circumferential burn	
Suspected child abuse	
Septic burn wounds	
Pre-existing medical disorder that could complicate management, prolong recovery or affect mortality (AIS =>3)	
Chemical burn	

Western Cape Guidelines

Criteria	Overrule (met or unmet)
<2 Year old	
Partial thickness >15%	
Full thickness >10%	
Inhalation injury requiring ventilation for more than 48 hours	
Suspected abuse	
Existing co-morbidity	
AIS >3	
Severe other injuries	
Special areas (face, hands, feet, genitalia, perineum, major joints, circumferential burns)	
Mechanism of injury (high pressure steam; HF acid; radiation; >1000V electricity	

SABS criteria summary

WCG criteria summary

APPENDIX 2. DATA COLLECTION FORM STUDY II

Tygerberg Hospital Burn Center Data collection

Additional Information

Patient data | Trauma info | Burn diagnosis | Disposition | Referral Criteria

Hospital record number

Case number in project

Payment group

City

Sex

Date Of Birth

Age

Weight

Date of injury

Time of injury

Admission
- Through the trauma unit
- Directly to the burns unit
- No information

Date of admission

Time of admission

Readmission
- Yes
- No

ICU admission
- Yes
- No
- No information

start date

end date

Length of stay ICU

Transport to Tygerberg
- Self/private
- Taxi
- EMS
- No information
- Police
- Other…

Referral Path
- Self-referred
- Brought directly by EMS
- Referred from other hospital (specify)
- No information
- Other…

Date of referral letter

Referral record number

Tygerberg Hospital Burn Center Data collection

Additional Information

Patient data | Trauma info | Burn diagnosis | Disposition | Referral Criteria

Mechanism
- Fire/flame
- Shack fire
- Paraffin
- Flash burns
- Hot object
- Hot water
- Hot oil
- Other hot liquid
- Steam
- Chemical
- Electrical
- High pressure steam
- High voltage electrical (>1000V)
- Hydrofluoric acid injury
- Exposure to ionizing radiation
- Motor-Vehicle Accident
- No information
- Other…

Intent
- Unintentional
- Intentional (Assault)
- Intentional (Self-harm)
- Unknown
- Other…

Circumstances (activity and place of injury)

Severe Associated Injury
- Yes (e.g. polytrauma, crush syndrome)
- No
- No information

Other non-burn injuries (Specify)

Pre-existing health illness (mark all that apply)
- HIV/AIDS
- TB
- Pregnant
- Depression
- Epilepsy
- Cancer
- Uncontrolled Type 1 Diabetes
- Existing psychiatric disorder
- Cardiac limitation and/or MI within 5 years
- Steroids or other immune-suppressing medication
- Respiratory limitation of exercise
- Alcohol/Drug consumption
- CVA/Stroke
- Hypertension
- None
- No information
- Other…

Tygerberg Hospital Burn Center Data collection

Additional Information

Patient data | Trauma info | Burn diagnosis | Disposition | Referral Criteria

Body part burned (mark all that apply)

- ☐ Head (excluding face)
  - ☐ Face
- ☐ Neck
- ☐ Upper extremities (excluding hands)
  - ☐ Hands
- ☐ Trunk/Back
- ☐ Trunk/Chest
  - ☐ Perineum
  - ☐ Genitalia
- ☐ Lower/extremities (excluding feet)
  - ☐ Feet

Indicate whether the burn was:

- ☐ Circumferential
- ☐ Septic burns (on presentation)
- ☐ Including major joints

Inhalation injury

- ○ Inhalation injury
- ○ Suspected inhalation injury
- ○ No
- ○ No information

Inhalation (comment)

Burn Unit diagnosis

Burn Depths

- ☐ Superficial
- ☐ Superficial Partial
- ☐ Mid Partial/Indeterminate
- ☐ Deep Partial
- ☐ Full
- ☐ No information

Most severe burn depth

- ○ Superficial
- ○ Superficial Partial
- ○ Mid Partial/Indeterminate
- ○ Deep Partial
- ○ Full
- ○ No information

TBSA at arrival

final TBSA

TBSA of Full thickness burn

ABSI score

○ Recorded ○ Not recorded

Referral diagnosis

Burn depth at referral

- ☐ Superficial
- ☐ Superficial Partial
- ☐ Mid Partial/Indeterminate
- ☐ Deep Partial
- ☐ Full
- ☐ No referral
- ☐ No information

TBSA at refferal

Burn Diagnosis Comments

Tygerberg Hospital Burn Center Data collection

Additional Information

Patient data | Trauma info | Burn diagnosis | Disposition | Referral Criteria

Treatment (mark all that apply)

Dressings

- ☐ Topical dressings
- ☐ Skin substitutes
- ☐ None
- ☐ No information

Surgery

- ☐ Escharotomy
- ☐ Debridement
- ☐ None
- ☐ No information
- ☐ Other…

Graft/Transplant

- ☐ Split skin graft (SSG)
- ☐ Full skin graft (FSG)
- ☐ Xenograft
- ☐ Allograft
- ☐ CEA
- ☐ None

Number of operations

IV-fluid (first 5 days)

- ☐ Yes
- ☐ Colloids (albumin)
- ☐ No
- ☐ No information

☐ Other Treatment

☐ Unknown treatment

Intubation

○ Yes ○ No ○ No information

Ventilator Start date | End date | Days on ventilator

Tracheotomy

○ Yes ○ No ○ No information

Infection

○ Yes ○ No ○ No information

Antibiotics used

☐ Empirical use ☐ Based on culture ☐ No

Multiple-resistant organism

○ Yes ○ No ○ No information

Septic shock

○ Yes (use of adrenaline) ○ No ○ No information

TB

○ Yes ○ No ○ No information

Pneumonia

○ Yes ○ No ○ No information

ARDS

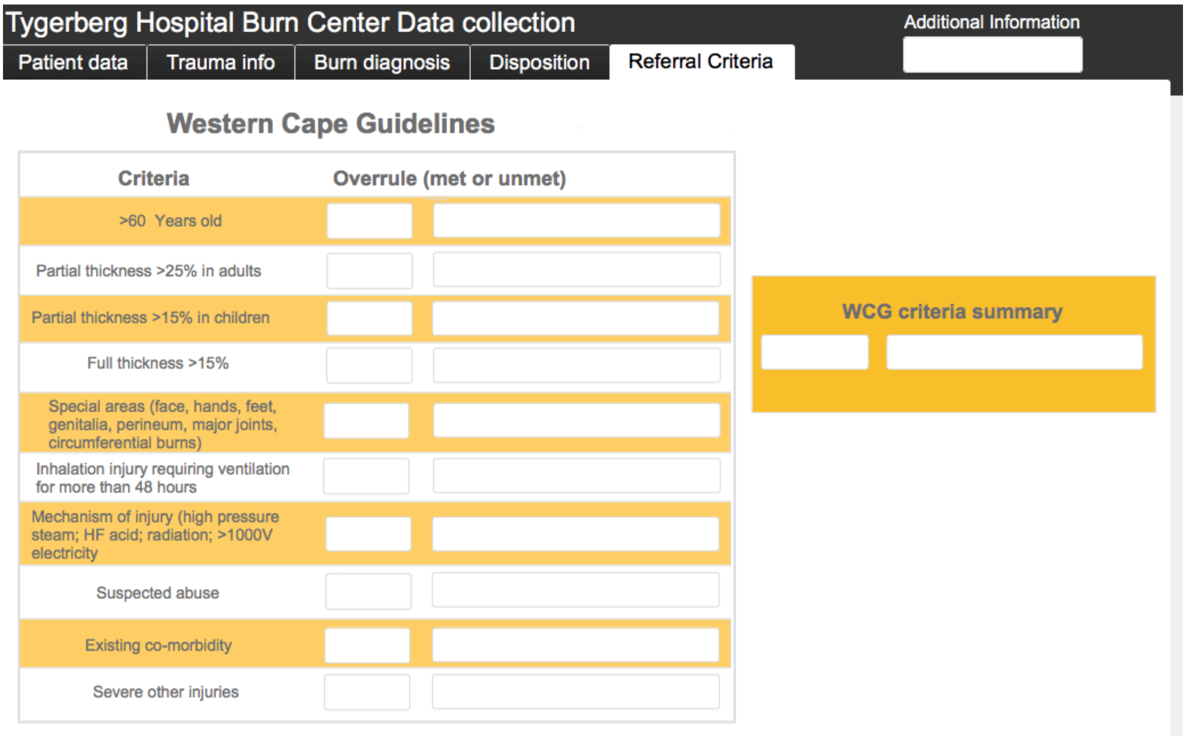
- ○ Yes
- ○ Mild
- ○ Moderate
- ○ Severe
- ○ No
- ○ No information

Dispostion at BURN UNIT

- ○ Discharged
- ○ Transferred to other hospital
- ○ Died
- ○ No Information
- ○ Other…

Date of discharge

Length of stay in days


Tygerberg Hospital Burn Center Data collection
Additional Information
Patient data
Trauma info
Burn diagnosis
Disposition
Referral Criteria
Western Cape Guidelines
Criteria
Overrule (met or unmet)
>60 Years old
Partial thickness >25% in adults
Partial thickness >15% in children
Full thickness >15%
Special areas (face, hands, feet, genitalia, perineum, major joints, circumferential burns)
Inhalation injury requiring ventilation for more than 48 hours
Mechanism of injury (high pressure steam; HF acid; radiation; >1000V electricity
Suspected abuse
Existing co-morbidity
Severe other injuries
WCG criteria summary

APPENDIX 3. ONLINE SURVEY STUDY III

moBurnZA Handheld Diagnosability

Device information

* 1. Please specify the type of device you are using to answer this survey:

- ◯ Smartphone
- ◯ Tablet

* 2. Please select the brand of the device:

* 3. Please specify the model of your device with as much details as possible:

* 4. How often do you use this type of device for image-based remote assessment?

- ◯ Every Day
- ◯ A few times a week
- ◯ Once a week
- ◯ A few times a month
- ◯ Once a month
- ◯ A few times a year
- ◯ Never

Personal information

* 1. What is your country of practice?

[ ]

* 2. What is your age?

[ ]

* 3. Please enter your medical qualification(s):

- ☐ Medical Officer
- ☐ Registrar
- ☐ Specialist Surgeon
- ☐ Specialist Emergency Physician
- ☐ Other Specialist

Other (please specify)

[ ]

* 4. How would you describe your experience with acute burn care:

- ○ Extensive
- ○ Moderate
- ○ Minimal
- ○ None

* 5. Please estimate the number of burns patients you have managed over the past 6 months:

[ ]

Example of one of the 51 cases:

Case

Description: 1 year old, female, hot water burn, right arm

* 1. Please choose the depth of this burn injury:

- Superficial partial thickness
- Mid partial thickness/indeterminate
- Deep partial thickness
- Full thickness
- Other (please specify)

* 2. What is the TBSA of this injury?

3. Additional comments

Confidence Assessment

* 1. Please rate your confidence in making a diagnosis from the images in this survey:

Completely Confident	Mostly Confident	Confidence varied depending on image	Poor Confidence	No Confidence
○	○	○	○	○

* 2. How comfortable would you be to use a telemedicine system, using similar images and information, for the management of burn patients in the future?

Completely Comfortable	Somewhat Comfortable	Somewhat Uncomfortable	Completely Uncomfortable
○	○	○	○

* 3. How helpful are images in making a diagnosis and providing advice in burn care?

Helpful	Images make no difference	Counter Productive
○	○	○

4. Please add any comments regarding your concerns (if any) regarding the diagnosis of the images in this survey