Long Term Mortality After Lower Extremity Amputation in South Africa

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DECLARATION

I, Salah Husein, hereby declare that the work on which this dissertation is based is my original work and that neither the whole work or any part of it has been, is being, or is to be submitted for another degree in this or any other university. I empower the university to reproduce, for the purpose of research, either the whole or any portion of the contents in of this work any manner whatsoever.

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Signature: Salah Husein
Date: 25 January 2019

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ABSTRACT

Introduction:

Long-term mortality after lower extremity amputation is not well reported in low- and middle-income countries. The primary aim of this study was to report 30-day and one-year mortality after lower extremity amputation in South Africa. The secondary objective was to report risk factors for one-year mortality.

Methods:

This was a retrospective cohort study of patients undergoing lower extremity amputations at New Somerset Hospital from October 1, 2015, to October 31, 2016. A medical record review was undertaken to identify co-morbidities, operation details, and perioperative mortality rate. Outcome status was defined as alive, dead, or lost to follow-up. Outcomes at 30 days and one year were reported.

Results:

There were 152 patients; 90 (59%) males and the median age (interquartile range, IQR) was 60 (54-67) years. At 30 days, 102 patients were traced and 12 (12%) were dead. At one year, 86 (57%) were traced and 37 (43%) were dead.

Conclusion

At this South African hospital, 43% of patients undergoing lower extremity amputations were dead after one year. In resource-constrained settings, mortality data are necessary when considering resource allocation for lower extremity amputations and essential surgical care packages.

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LITERATURE REVIEW

1. Background

Amputation is the surgical removal of all or part of a limb or extremity. The word amputation is originally derived from the Latin *amputare*, which means "to cut away". Amputation is an old surgical procedure and was described as early as 1700 BC. Furthermore, Rig-Veda recorded the first amputation and prosthesis done for the leg of Queen Vishpla, where an iron leg was fitted after wound healing to allow mobility and returning back to the battlefield in the second millennium BC.[1] However, amputation was more commonly performed for criminal punishment and not routinely performed for medical reasons until the 17th century after which, the English word "amputation" became an accepted medical term.

2. Incidence

Lower extremity amputation (LEA) is much more common than upper extremity amputation. LEA is a common general, vascular, or orthopaedic surgical procedure. It is challenging to determine the prevalence as many countries do not record amputations. There are variations in LEA incidence worldwide. LEA is due to a variety of factors but diabetes mellitus (DM) and its associated complications are major contributors in patients requiring LEA.[2] The introduction of specialized diabetic foot care clinics[2] and vascular interventions[3,4] can help delay LEA. However, often LEA is still needed despite vascular intervention.[5,6] Furthermore, the rate of LEA remains unchanged in the past two decades. This is partly due to an ageing population and therefore rise in atherosclerosis, DM, and peripheral vascular disease (PVD).[7,8,9] In high income countries (HICs) such as the United States (US), approximately 185,000 persons undergo LEA annually.[10] However, in South Africa there are no publications of lower limb amputations epidemiology.[11]

3. Level of Amputation

Minor LEAs are ones below the ankle such as toe removal (known as Ray's amputation), and trans metatarsal amputation (TMA). LEAs above the ankle are considered major amputations and include supramalleolar amputation (SMA), below the knee amputation (BKA), and above the knee amputation (AKA).

The level of LEA depends on the level of arterial disease and/or the location of the soft tissue lesion or sepsis. The determination of the level of LEA is usually based on clinical examination to determine the degree of the disease, potential wound healing based on blood supply, extent of sepsis, and consideration of rehabilitation options.[12,13]

In a study from Amsterdam, 90% of AKA and 80% BKA resulted in good wound healing based on clinical decisions without need for additional radiologic tests.[14] While preservation of limb length is desirable, excision and removal of dead and infected tissue are more important. If the clinical assessment is not sufficient to determine the level of amputation, there are other tests such as skin perfusion pressure, transcutaneous oxygen measurements, and ankle and toe pressure tests. However, due to their low sensitivity for wound healing prediction, they must be used as an addition and cannot replace clinical assessment.[14,15,16]

4. Emergency LEA

Emergency amputation can be performed in one step or two steps (also known staged operation). In a one-step procedure, a formalized surgical amputation is performed. In a staged operation, the first step is a guillotine amputation for sepsis control and the second is the formalized surgical amputation which considers the future rehabilitation and patient mobility. In surgical practice, a guillotine amputation is an amputation performed in an urgent setting as a quick procedure without closure of the skin. Typical indications include infection control due to infected gangrene (wet or gas gangrene) and catastrophic trauma from a severely crushed limb. LEA can be performed electively if the patient is hemodynamically stable, systemically not septic, and the existing sepsis can be controlled with simple drainage of abscess or debridement of necrotic tissue combined with antibiotic cover. In patients with sepsis that cannot be controlled locally, an emergency LEA should be carried out without delay.[17,18]

5. Indications for LEA

In HICs, the main indications are vascular disease, DM, and peripheral arterial disease (PAD), trauma, and less commonly, cancer.[10] Advanced DM and PAD can result in an unsalvageable limb (without an option of revascularization), severe infection after failed treatment, or patients with medical risk factors that contraindicate revascularization.[19]

DM is a significant risk factor for LEA. Poorly controlled blood sugar aggravates vascular damage, that results in organ blood flow reduction, and indirectly reduces the efficacy of the immunity by reducing the chemotactic mechanism and phagocytic function. In addition, DM results in peripheral neuropathy which affects motor and sensory function. The small joints of the foot are susceptible to deformity that increases the chance of trauma especially from tight shoes, as there is a sensory defect. The small injuries cannot be detected until they get infected. Furthermore, the infection is difficult to control because of impaired blood flow that impedes the normal defence mechanism, making dead tissue a good media for pathogen proliferation and spread to healthy tissue.[20,21]

PAD affects the arterial supply to limbs, leading to narrowing or obstruction of the blood vessels and ischemia of the limb. Older age, hypertension, tobacco use, diabetes, hypercholesterolemia, and atherosclerosis are well-known risk factors for the development of PAD.[22,23] Specifically, atherosclerosis is notable risk factor. It can lead to thromboembolic disease, affecting the blood supply and contributing to risk of LEA.

Trauma is the second most common indication for LEA. LEA is performed when limb salvage cannot be done due to compartment syndrome, massive tissue destruction, or for uncontrolled bleeding. LEA can be performed for penetrating and blunt trauma including road traffic accidents, other severe accidents such as electric shock.[24],[25]

Bone and soft tissue cancers that cannot be managed with local resection, radiotherapy, or chemotherapy may require LEA.[26] Other indications include, debilitating extremity paralysis and severe deformity (e.g. paraplegia) from infection or pressure-related complications. [27]

Historically, traumatic injuries were the leading cause of LEA in low- and middle- income countries (LMICs);[28],[29] however, as non-communicable diseases (NCDs) in LMICs are increasing and infectious diseases are still prevalent, these nations are facing a double burden of medical indications for LEA.[30]

Amputation is indicated if revascularisation is considered inappropriate in bedridden patients, in a functionally useless limb, in patients with life threatening sepsis, extensive muscle necrosis and where it is technically impossible. Primary amputation is better in these cases.[31,32]

6. LEA Procedures

Amputation procedures can be performed using different kinds of anaesthesia based on the level of amputation and general patient condition. The operation can be performed under local anaesthesia or nerve block for minor amputations such as Ray's amputation, and regional, spinal, and general anaesthesia for higher levels. Amputations are composed of different steps starts with bleeding control by ligating the supplying artery and vein, muscle transaction, and bone cutting. The bone should be covered with skin and muscle flap created during the procedure. The choice of a procedure is based on the clinical examination. In select cases when the choice of operation cannot be made on clinical examination alone, duplex ultrasound, digit photoplethysomgraphy, and transcutaneous measurement of oxygen pressure can aid in determining the choice of operation.[33],[34] In some cases, revascularization or angioplasty is considered based on patient and disease condition, and when facilities, equipment and skilled vascular surgeons are available.

7. Post-Operative Complications After LEA

Surgical procedures can result in early or late (30-day, or later respectively) postoperative complications depending on the type of surgery and pre-existing patient risk factors. One early complication is the need for re-operation because of a non-healing wound stump due to impaired blood flow. LEA associated with sepsis, end-stage renal disease, systemic inflammatory response syndrome, a body mass index greater than 30, intraoperative surgical trainee participation, and smoking are usually factors that lead to additional amputation(s).[35] Furthermore, the more distal the amputation, the more likely the chance for higher amputation in the future.[33'34] If local sepsis is not adequately controlled, this could lead to complications including, superficial infection, deep infection, bleeding stump, and/or wound breakdown. Sepsis may progress in severity from local infection and bacteremia to septic shock, resulting in multiple organ dysfunction syndromes (MODS) and death. In acute respiratory distress syndrome (ARDS) as a result of severe organ dysfunction, disseminated intravascular coagulation (DIC), or acute kidney injury (ALI), there is an increase in the mortality rate based on the severity of sepsis.[22] Septic shock and thrombocytopenia are independent risk factors for in-hospital mortality following AKA.[36],[37]

Cardiac complications, sepsis, and pneumonia are the main causes of perioperative mortality following LEA for patients with PAD.[38],[39] Postoperative lung complications are a common

cause of morbidity and mortality. Pneumonia and atelectasis account for most of these complications. Pneumonia is one of the most common causes of post LEA 30-day mortality. Pulmonary complications can be reduced by good postoperative pain control and physiotherapy.[38,39] Other complications after LEA include surgical site infection, hematoma, deep venous thromboembolism, atelectasis, and pneumonia.[40]

8. Post-Operative Mortality

Post-operative mortality is usually reported as peri-operative mortality rate (POMR), 30-day (30DM), one-year (1YM), or five-year mortality (5YM). The (POMR) is defined as death in the operating theatre or prior to discharge. Early mortality is defined as death within 30 days and late mortality is death one-year or later after operation.[41]

Long-term mortality after LEA is high in HICs. Large series studies from HICs report 30DM from 9- 30%,[42,43] and a meta-analysis demonstrated a 48% 1YM.[44] In the 1960s and 1970s, some sites reported early mortality as high as 40%,[45,46,47] but more recent studies reported rates between 3-18%,[33,17,48,49] with one systematic review reporting 22% early mortality.[50] 1YM has been reported as 20-35% following BKA, and 40-50% after AKA.[33,17,49,51] Mortality is higher in diabetic patients and those on regular dialysis.[49] For those with vascular disease, nearly all were dead at five years.[52]

Long-term mortality after surgical procedures is not easily measured in LMICs given the lack of systematic post-operative follow-up. POMR is known to be higher than in HICs especially after emergency procedures.[53] In a systematic review from Nigeria, POMR was reported as 11% although 30DM and 1YM were not captured.[29] A systematic review of all LEA for DM in Africa reported a 14% POMR.[54]

9. Risk Factors for Mortality after LEA

Emergency versus Elective

Emergency LEA is associated with higher mortality than electives LEA. A delay in performing an emergency LEA increases POMR by 2% for every day of delay.[50] A guillotine amputation, which is often performed in an emergency setting compared with an elective

setting, is associated with increased 30-day postoperative mortality.[17] The 30DM rate in a study from the US was 14% for guillotine amputation and 8% for one step amputation.[17]

Level of amputation

Mortality following minor lower limb amputation is 2-7%.[55,56] However, a minor amputation is often followed by a subsequent major amputation, which is associated with increased mortality. The higher the level of amputation, the greater the mortality. For example, one meta-analysis reported the mortality rate for BKA was 7% compared with 13% for AKA.[44] The association between the higher level of amputation and the higher mortality rate may be related to the severity of the indication, rather than the operation itself.[44]

Primary versus Secondary

A primary amputation is when no prior intervention has been performed, while secondary amputation is an amputation following a failed operative attempt to salvage the limb. Limb revascularization and endovascular angioplasty reduces the rate of major LEA, but increases the rate of minor amputations. The 30DM is lower after revascularization compared with without revascularization.[38,57]

Comorbidities associated with LEA

Comorbidities such as DM, arteriosclerosis, coronary artery disease, cerebral vascular disease, and end-stage renal disease increases post-operative mortality after LEA.[17,44,58]

Peripheral arterial disease and coronary arterial disease

PAD is a common risk factor for amputation. This is because PAD leads to chronic limb ischemia, which can result in severe pain, gangrene, or sepsis, which are indications for amputation.[59] PAD and coronary arterial disease (CAD) are strongly correlated.[60] Amputation in a patient with cardiovascular disease is associated with increased peri- and post-operative morbidity and mortality,[61] largely a result of cardiac complications.[54]

Diabetes mellitus

DM contributes to the need for LEA. A study in Cape Town, South Africa found that majority of LEA performed were for patients with DM. People with DM were more likely to require multiple LEA and operations.[62] Long-standing and poorly-controlled DM causes diabetic nephropathy and impaired kidney function, atherosclerosis, ischemic heart disease, and intra- and extra-cranial cerebrovascular disease; all of which are associated with higher morbidity and mortality. In diabetic patients, the risk of PAD and ischemic events is higher compared with non- diabetic patients.[63]

In one study, there was no difference between AKA and BKA in both early and late postoperative mortality among diabetic patients.[39] However, another study found significant differences between the two amputation levels. The 1YM was 43% for AKA and 25% for BKA, and the 5YM was 66% in BKA and 83% in AKA.[64]

Diabetic patients who developed diabetic nephropathy with end stage renal disease (ESRD) are at risk of major post-LEA complications, especially if the indication of the amputation is sepsis.[65] However, random blood sugar level has no effect on the outcomes of 30-day LEA.[66]

Smoking

Smoking diabetic patient usually undergoes more amputations compared with a non-smoking diabetic patient.[61] The impact of smoking is exacerbated by the number of cigarettes and duration. Furthermore, smoking is associated with delayed wound healing.[67] In relation to mortality after amputation, smoking leads to chronic obstructive pulmonary disease (COPD), PAD, and cardiovascular disease, which increases mortality.[68]

Renal impairment

Renal failure increases postoperative mortality by threefold in patients undergoing LEA.[69]

Immunosuppression and malnutrition

The use of steroids and immunosuppressive medication, and low albumin levels are recognized risk factors for delayed wound healing. They also increase the risk of surgical site infection, post-operative morbidity, prolonged hospital stay, and post-LEA mortality.[58,69]

Trauma-related LEA

Historically, traumatic injuries were the leading cause of LEA in LMIC.[28,29] LEA as a result of isolated lower extremity injuries has a lower mortality rate than polytrauma. Often, mortality due to trauma is related to concomitant organ injuries including head injuries, torso, and pelvic injuries. The mortality rate after LEA is higher with blunt trauma compared with penetrating trauma. In blunt extremity injuries among civilians, mortality is 5-10%.[24,25]

Age

Age greater than 80 years old is a risk factor for increased LEA postoperative mortality.[43,69]

10. Decreasing Mortality after LEA

Appropriate medical management may play a role in reducing the morbidity and mortality of LEA. The best results following LEA are achieved through a multidisciplinary approach. This involves physiotherapy for rehabilitation, and improved mobility with the use of walking aids or prosthesis. Pain management and reduction of postoperative risk of complications, such as pulmonary complications is important. In addition, the role of psychological treatment is crucial, as there is a risk of developing post amputation depression. Furthermore, social workers and occupational therapists are involved to support and help with potential physical disability resulting from losing one limb or more.

A multidisciplinary approach helps reduce the 30DM post-LEA. Preoperative assessment, identification of medical risk factors and appropriately addressing them, and nutritional assessment should proceed any amputation to reduce postoperative morbidity and mortality.[33]

Statins are recommended by vascular surgeons as part of the best medical treatment plan for patients with PAD. They are the drugs of choice to reduce high blood cholesterol, which is a risk factor for cerebrovascular disease. Statin use is associated with reducing all- cause mortality, cardio and cerebrovascular events, and the rate of revascularization. Statin treatment reduced mortality caused by coronary artery disease, cardiovascular disease, cerebrovascular disease.[70] In terms of LEA, statin therapy reduces 90 day or more mortality but there is no association with early (30-day) mortality.[71]

Appropriate medical management plays a role in reducing the morbidity and mortality burden of LEA. Among a cohort of elderly vulnerable patients with medical comorbidities who are at high risk of early postoperative mortality, a multidisciplinary approach reduced the 30DM post-LEA from 40-10%. The multidisciplinary approach included an experienced physician, comprehensive evaluation of risk factors, no delays in surgical care, and availability of post-operative elderly care unit.[72]

11. LEA as an Essential Procedure

As discussed, LEA is a crucial procedure. However, LMICs often have health systems with limited resources. In these countries, best buys, or interventions that can achieve the greatest health impact with available resources, need to be prioritized when choosing the basket of procedures to be included in essential regional and national surgical packages.[73]

LEA is an expensive procedure and a large number of patients need it. There is a paucity of data on the cost of LEA in LMICs. In the UK, a prospective study looked at the cost of surgical intervention to salvage or amputate the limb, with the results demonstrating that primary amputation is £10,162, with additional potential costs of: reconstruction (£6,766), angioplasty (£6,611), and revascularization (£3,970). However, a notable cost of LEA is the prolonged hospital stay and rehabilitation.[74]

However, several factors beyond direct cost are needed to set surgical priorities including quality-adjusted life years gained, indirect costs to the health system and patient, and post-operative outcomes such as mortality. Ease of suffering and respect and dignity are also issues of concern when assessing the impact of an intervention.[73,75] There is a need for data and research on these various factors to help determine if procedures are a “best buy.”

12. Summary

LEA is a common operation worldwide and associated with significant early and late post-operative mortality. Vascular disease caused by PAD and DM is the most common indication for LEA. Trauma is a more common indication in LMICs than in HICs. Risk factors for mortality include higher level of amputation, PAD, DM, and other pre-existing comorbidities. However, long-term mortality after LEA is not well reported in LMICs. The primary aim of this study was to report 30-day and one-year mortality after LEA in South Africa. The

secondary objective was to report risk factors for one-year mortality. Mortality data are an important part of determining if a procedure is a best buy in LMICs.

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2. PUBLICATION READY MANUSCRIPT

1. Title page

Long Term Mortality After Lower Extremity Amputation in South Africa

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Main text word count: 1491

2. Abstract

Abstract

Introduction

Long-term mortality after lower extremity amputation is not well reported in low- and middle- income countries. The primary aim of this study was to report 30-day and one-year mortality after lower extremity amputation in South Africa. The secondary objective was to report risk factors for one-year mortality.

Methods

This was a retrospective cohort study of patients undergoing lower extremity amputations at New Somerset Hospital from October 1, 2015, to October 31, 2016. A medical record review was undertaken to identify co-morbidities, operation details, and perioperative mortality rate. Outcome status was defined as alive, dead, or lost to follow-up. Outcomes at 30 days and one year were reported.

Results

There were 152 patients; 90 (59%) males and the median age (interquartile range, IQR) was 60 (54-67) years. At 30 days, 102 patients were traced and 12 (12%) were dead. At one year, 86 (57%) were traced and 37 (43%) were dead.

Conclusion

At this South African hospital, 43% of patients undergoing lower extremity amputations were dead after one year. In resource-constrained settings, mortality data are necessary when considering resource allocation for lower extremity amputations and essential surgical care packages.

Key words: surgery, amputation, post-operative mortality, health systems strengthening

3. Text of Article

Introduction

Surgical care can prevent disability and save millions of lives per year.[1] Surgical care is known to be cost-effective and in 2015, the World Health Assembly declared that essential and emergency surgical procedures should be part of universal health care.[2] The majority of the surgical burden is in low- and middle- income countries (LMICs) which have health systems with limited resources.[1] In these countries, best buys, or interventions that can achieve the greatest help impact with the available resources, need to be considered when choosing what procedures are included in essential national and regional surgical packages.[3] Procedures with high mortality rates may not be ideal to include. Knowing the long-term survival after specific surgical procedures in each setting provides important information for policymakers as they determine essential surgical packages.

Mortality after surgical procedures is not easily measured in LMICs given the lack of systematic post-operative follow-up. Peri-operative mortality (POMR) or in-hospital mortality is known to be higher in LMICs than in high-income countries (HICs), especially after emergency procedures.[4]

In HICs, lower extremity amputation (LEA) is a common general surgical procedure for end-stage complications of the peripheral vascular disease (PVD) and diabetes mellitus (DM).[5,6] Historically, traumatic injuries were the leading cause of LEA in LMICs;[7,8,9] however, as non-communicable diseases (NCDs) in LMICs are increasing and infectious diseases are still prevalent, these nations are facing a double burden of medical indications for LEA.[10] In a study from Cape Town, South Africa, the most common cause of non-traumatic LEA was DM.[11]

Long-term mortality after LEA is high in HICs. Studies from HICs report 30-day mortality to be 9-30%[12,13] and a meta-analysis demonstrated a 48% 1-year mortality (1YM) among patients with PVD and DM.[14] The most common causes of death after

amputation are cardiac complications.[15] Risk factors for death after LEA include surgical factors such as higher level of amputation, the need for staged procedures, as well as associated co-morbidities such as age >80 years, preoperative sepsis, DM, arteriosclerosis, coronary artery disease, cerebral vascular disease, and end- stage renal disease.[14,16,17,18]

In LMICs, there is a paucity of data describing long-term mortality after LEA and associated risk factors. In a systematic review from Nigeria, POMR was reported at 11% although 30-day and 1YM were not captured.[9] A systematic review of all LEA for DM in Africa reported a 14% POMR.[19] Long-term mortality after LEA is one factor considered when determining best buys for essential surgical packages in resource-limited settings. The primary aim of this study was to report 30-day and 1YM after LEA from an upper middle- income country, South Africa. The secondary objectives were to report risk factors for 1YM.

Methods

Study design and period

This was a retrospective cohort study of patients undergoing LEA at New Somerset Hospital (NSH) from October 1, 2015, to October 31, 2016.

Study population

NSH is a second-level government hospital in Cape Town, South Africa which serves a catchment population of approximately 500,000 persons. Major extremity trauma cases are referred to a third- level hospital, Groote Schuur Hospital, approximately 10km away. All patients undergoing LEA at NSH during the study period were included. Patients undergoing upper extremity amputations, or non-amputation procedures concomitant to LEA, were excluded. Patients under 18 years of age were also excluded.

Ethics approval

Ethics approval was given by the University of Cape Town Human Ethics Committee.

Data collection

A hospital operative electronic database used for routine monitoring and evaluation was queried to identify eligible patients and operative characteristics. A medical record review was undertaken to identify co-morbidities and mortality. The following patient demographics and co-morbidities were captured: age, gender, PVD, DM, hypertension (HTN), smoking status, and previous LEA on a contralateral limb. Surgical variables included: type of LEA, trauma, and multiple LEA (more than one amputation on the same limb during the study period). Type of LEA included toe, trans-metatarsal, supra-malleolar (Guillotine), below knee (BKA), and above knee amputations (AKA). The level of amputation depended on the level of vascular disease or injury. Clinical criteria were used for many patients rather than vascular imaging due to limited resources. Revascularization and angioplasty were available at the third-level hospital and prospective candidates were referred there prior to decision for amputation. In this resource-limited setting, people with multiple comorbidities disease distal to the popliteal fossa were usually not considered candidates for revascularization and angioplasty. Outcome status was defined as alive, dead, or lost to follow-up (LTFU). Outcome status was obtained from three sources. First, patients or their next of kin were traced telephonically after giving verbal consent during two tracing episodes: March-April 2017 and August 2018. For each tracing episode, three attempts were made to contact each patient/next of kin. Second, a search for deaths at Western Cape government hospitals using a centralized computerized administration system (CLINICOM) was undertaken.[20] [20] Finally, deaths of patients with South African identification numbers (through March 16, 2018) were identified through the National Population Register. Patients not traced and/or were not confirmed dead were considered LTFU. 30- day mortality was defined as death within 30 days of LEA. If more than one LEA was performed during the study period, mortality was calculated from the last procedure. 1YM was defined as death within 365 days of the last LEA.

Statistical analysis

Descriptive statistics were used to describe patients' and operative characteristics. Univariate and multivariate analysis were performed to find associations with 1YM. Age and gender were included *a priori* and all other variables with a p value<0.2 on univariate analysis were included in the multivariate analysis. Previous and multiple LEA were combined into one variable. The data were de-identified before analysis and all databases were security encoded.

Results

There were 152 patients; 90 (59%) males and the median age (interquartile range, IQR) was 60 (54-67) years. Co-morbidities were available for 137 (90%) of the cohort. Of these, 108 (79%) had PVD and 91 (66%) had DM. Majority of patients had gangrene (89%), with half having wet gangrene and the other half dry gangrene. Fifty-three (35%) had a prior LEA on the same or the contralateral limb or a second LEA during the study period. Only 4 (3%) LEA were performed for traumatic injury. Patient demographics are shown in Table 1.

Operative Characteristics

There were 183 LEA in 152 patients. The most common LEA was AKA (n=104, 57%), followed by BKA (n=36, 20%). See Table 2.

O*utcomes*

At 30 days, 102 (67%) of 152 were traced. Of these 12 (12%) were dead. At one year, 86 (57%) were traced. Of these, 37 (43%) were dead. At the end of the study, there was a median follow-up time of 522 (interquartile range: 190-801) days. A Kaplan Meier survival curve is shown in Figure 1.

Associations with One Year Mortality

On univariate analysis, age ≥ 75 years of age, male gender, and AKA were associated with 1YM and included in the multivariate analysis (Table 3). On multivariate analysis, age≥ 75 years (OR 7.81, p=0.017) were associated with 1YM. See Table 3.

Discussion

At this second- level government hospital in South Africa, 40% of patients undergoing LEA were dead after one year. While this proportion is high, it is lower or consistent with the rates in some HICs.[14],[21] Additionally, age was a risk factor for death after LEA.

Only 3% LEA were performed for traumatic injury. While, trauma is a major contributor to LEA in LMICs, at this second-level hospital, trauma patients were usually referred to a third level hospital for specialized care.

In our study, most LEA patients had a prior history of HTN, PVD, DM, or smoking without preceding trauma. Furthermore, majority of patients had gangrene with half presenting with wet gangrene. Therefore, long-term mortality after LEA is not surprising given these major co-morbidities. While our study did not report cause-specific mortality, other studies have shown that cardiac complications from microcirculation and vascular perfusion damage are the most common causes of death after LEA.[15]

South Africa is rolling out a National Health Insurance plan and will likely include an essential basket of surgical procedures.[22] Given the resource limitations in LMICs, each surgical procedure needs to be evaluated to determine if it is a "best buy". Several factors are needed to set surgical priorities including quality-adjusted life years gained, indirect and direct costs to the health system and patient, and post-operative outcomes.[3] Ease of suffering and respect and dignity are also issues of concern when assessing the impact of an intervention.[23] This study is significant in

that it demonstrates long-term mortality after LEA can be high and therefore impacts its value as a "best buy" under universal health coverage for South Africa.

This was a retrospective manual review of secondary data. The data is subject to memory or registry bias. There are additional factors and comorbidities, and the causes of mortality that may be important in the risk factor analysis but were unavailable at the time of data collection. Furthermore, a longer time period would have likely resulted in a larger sample size and increased statistical power. One limitation of our study was that one-third of our patients were LTFU at 30 days and more than 40% by one year. It is likely that a large proportion of LTFU patients were actually alive since they were not recorded as dead in CLINCOM nor the National Population Registry. Therefore, 30- day mortality may have been as low as 8% and 1YM 24% if all LFTU were considered alive. In addition, cost data, which are important in determining best buys, were not evaluated in this study.

Conclusion

At New Somerset Hospital in Cape Town, South Africa, up to 43% of patients were dead one year after LEA. Long-term mortality needs to be considered when deciding which surgical procedures should be considered in universal health coverage in national surgical planning.

What is already known on this topic

- Lower extremity amputation (LEA) is a common surgical procedure;
- Long-term mortality after LEA is high in high income countries;
- There is a paucity of data describing long-term mortality after LEA and associated risk factors in lower to middle-income countries.

What this study adds

- One-year mortality after LEA in a government hospital in South Africa, an upper-middle income country, was 43%;

- The results from this study provide useful data to define the appropriate basket of surgical procedures for universal health coverage in resource-limited settings.

Competing interests

Heather Bougard consults and provides proctorship for BD / BARD and Medtronic. The remaining authors have no interests to declare.

Authors' contributions

SH, study conceptualization, data collection, drafting of manuscript and approval of final manuscript. HB, study conceptualization, critical review of manuscript, and final approval of manuscript. KC, study conceptualization, data analysis, drafting of manuscript, and approval of final manuscript.

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5. Tables and Figures

Table 1: Patient characteristics of lower extremity amputation at a second-level government hospital in South Africa

	n (%)
Total cohort	152
Mean age (interquartile range)	60 (54-67)
Males	90 (59)
Co-morbidities *	
Peripheral vascular disease	108 (79)
Hypertension	95 (69)
Diabetes	91 (66)
Smoking	70 (51)
Operative indications	
Gangrene	135 (89)
Wet	67 (50)
Dry	68 (50)
Trauma	4 (3)
Multiple lower extremity amputation **	53 (35)

* n=137
** more than one LEA on the same or contralateral limb

Table 2: Types of lower extremity amputation performed at a second-level government hospital in South Africa

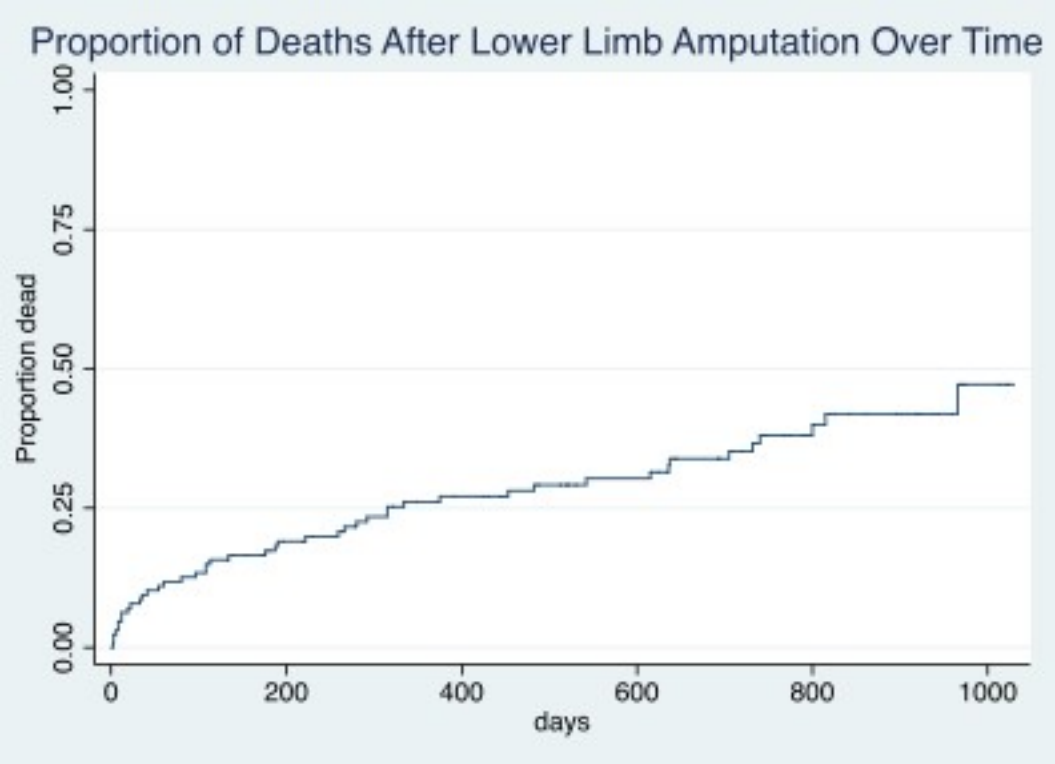
Procedures	N (%)
Above knee amputation	104 (57)
Below knee amputation	36 (20)
Toe amputation	19 (10)
Supra-malleolar amputation	18 (10)
Trans-metatarsel amputation	6 (3)
Total	183 (100)

Table 3: Risk factors for one-year morality after lower extremity amputation

	Univariate Analysis			Multivariate Analysis		
	OR	**Confidence Interval**	**P Value**	**OR**	**Confidence Interval**	**P Value**
Demographics						
Age ≥75 years	6.43	1.29- 32.05	0.023	7.81	1.45- 42.20	0.017
Male gender	1.89	0.76- 4.74	0.172	2.15	0.80- 5.77	0.129
Co-morbidities						
Peripheral vascular disease	1.32	0.39- 4.48	0.659			
Hypertension	1.33	0.49- 3.62	0.573			
Diabetes mellitus	0.97	0.38- 2.51	0.954			
Smoking	1.23	0.49- 3.09	0.654			
Operative Indications						
Wet gangrene	1.30	0.51-3.28	0.582			
Trauma	2.34	0.20- 26.95	0.494			
Operation						
Above knee amputation	2.14	0.75- 6.08	0.152	2.35	0.77- 7.20	0.134
Below knee amputation	0.44	0.12- 1.59	0.212			
Supra-malleolar amputation	1.00					
Trans-metatarsal amputation	1.14	0.15- 8.54	0.896			
Toe Amputation	1.00					
Multiple lower extremity amputation*	0.54	0.21- 1.41	0.211			

OR, odds ratio
*more than one LEA on the same or contralateral limb
Risk factors with a p value <0.2 on univariate analysis were included in the multivariate analysis

Figure 1: Deaths over time after lower extremity amputation at a second-level government hospital in South Africa



3. STUDY APPROVAL DOCUMENTATION

UNIVERSITY OF CAPE TOWN
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09 November 2016

HREC REF: 709/2016

Dr K Chu
Surgery
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OMB

Dear Dr Chu

PROJECT TITLE: RISK FACTORS FOR 30-DAY MORTALITY AFTER LOWER EXTREMITY AMPUTATION AT NEW SOMERSET HOSPITAL (MMED CANDIDATE - DR S HUSEIN)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the proof of concept for phase 1 of the above-mentioned study.

Approval is granted for one year until the 30th November 2017.

Please refer to the correct name for the UCT Faculty of Health Sciences Human Research Ethics Committee in the informed consent form.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Dr S Husein will be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS011: Study deviation

HREC office use only (FWA00001637; IRB00001938)			
This serves as acknowledgement of a protocol deviation as described below.			
Chairperson of the HREC signature	pp UBurgess	Date	12\12\2018

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	05/12/2018
HREC REF Number	709/2016
Project Title	Risk factors for 30-day mortality after lower extremity amputation at New Somerset Hospital
Protocol number (if applicable)	
Principal Investigator	Kathryn Chu
Department / Office Internal Mail Address	Kathryn.chu@uct.ac.za

2. Protocol deviation description

Please describe the deviation below, including the reason why the deviation occurred.
Project finished but MMED has not been submitted. Paper submitted to peer-reviewed journal awaiting outcome.

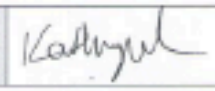
HUMAN RESEARCH ETHICS COMMITTEE
11 DEC 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

3. Follow-up actions

3.1 Please describe any follow-up action(s) taken or planned as a result of this deviation e.g. DSMB reporting, report to sponsor, informing participants.
None, just need the extension of HREC to be able to submit the MMED
3.2 Please describe what action(s) have or will be taken to prevent similar deviations in future.
Not allowing the HREC approval to lapse before the MMED is summitted

4. Principal Investigator's acknowledgement of responsibility

This signature indicates the PI has reviewed the deviation, taken appropriate follow-up action and implemented or plans to implement preventative steps where possible.

Signature of PI		Date	05/12/2018

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FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/12/19
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	pp	Date Signed	12/12/2018

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	05/12/2018		
HREC REF Number	709/2016	Current Ethics Approval was granted until	30/11/2017
Protocol title	RISK FACTORS FOR 30-DAY MORTALITY AFTER LOWER EXTREMITY AMPUTATION AT NEW SOMERSET HOSPITAL		
Principal Investigator	KATHRYN CHU		
Department / Office Internal Mail Address	Kathryn.chu@uct.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	✓ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
✓	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

709/2016

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3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		152
Total number of records or specimens collected, reviewed or stored since last progress report		152
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	✓ No

4. Signature

Signature of PI	Kathryn	Date	05/12/2018

4. PUBLICATION INSTRUCTIONS TO AUTHORS

Pan African Medical Journal

1. General

PAMJ is an online open access peer-reviewed journal. Authors are encouraged to submit original research, systematic review and short reports from the field of medicine and public health in Africa.
Prior to submit your first article, you should apply for a user name and password. PAMJ offers a user friendly process for online submission.

Short reports will include case report, commentary, conference proceedings, editorials, viewpoints, and letter to the editors. Short Communications should be no longer than 1500 words. They must have an abstract and references, but the main body of the text does not have to follow the original research's format. We give privilege to invited reviews and encourage prospective authors of systematic reviews to discuss the project with the editorial office before development.

After initial screening, which takes only a few days, manuscripts are sent to two-three referees. If appropriate, a statistical reviewer is involved. On average, we will report back to authors within 4-6 weeks with a first decision.

Manuscripts must be submitted by one of the authors of the manuscript, and should not be submitted by anyone on their behalf. The submitting author takes responsibility for the article during submission and peer review.

Languages of publication are English and French. Each author should provide an abstract of his article in the other language prior to submission. Poor English of French do not prevent acceptance provided the paper's content is of high scientific quality. All accepted manuscripts are copy-edited.

To facilitate rapid publication and to minimize administrative costs, PAMJ accepts only online submission. The submission process is compatible with version 3.0 or later of Internet Explorer, Opera, and Netscape Navigator.

Files can be submitted as a batch. The submission process allows the authors to interrupt it at any time, and continue where they left off at their return on the site.

During submission you will be asked to provide a cover letter. Use this to explain why your manuscript should be published in the journal and to elaborate on any issues relating to our editorial policies detailed in the instructions for authors.

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2. Submission of a paper Online submission

Authors may submit article to Pan African Medical Journal online. Simple onscreen instructions are provided.

Submission by email

Authors may submit article by email if the have limited or unstable Internet connection. Articles and associated material should be sent to any of the following email address:

• submission@panafrican-med-journal.com **Conflict of interest**

Will be mentioned in the manuscript as "Authors declared they have no conflict of interest". The editorial office will acknowledge receipt of all manuscripts by email

3. Organization of a full-length paper

Download the journal manuscript template.

Maximum length: 4000 words in main text (i.e., excluding abstract, references, legends, tables and figures), 6 tables/figures, and a structured abstract of 250 words plus up to 50 references.

Title page – This page should states: a) The title of the paper (include the study design if appropriate; for example: A versus B in the treatment of C: a randomized controlled trial; X is a risk factor for Y: a case control study), b) Authors names (full name – no qualification), c) institution(s) of origin, d) Corresponding author plus his/her address, telephone and fax number, e-mail address, e) Word count (for both abstract and the main text)

Abstract - The abstract of the manuscript should not exceed 250 words and must be structured into separate sections: **Background:** the context and purpose of the study; **Method:** how the study was performed and statistical tests used; **Results:** the main findings; **Conclusion:** brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract.

Keywords. Up to ten keywords (suitable for Index Medicus listing) should be provided at the end of the Abstract. **Abbreviations** Please do not provide a list of abbreviations. Abbreviations should be spelled out the first time they appear in the text.

Background The background section should be written from the standpoint of researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature

Method Sufficient information should be given to permit repetition of the experimental work. This should include the design of the study, the setting, the type of participants or materials involved, a clear description of all interventions and comparisons, and the type of analysis used, including a power calculation if appropriate.

Results - The Results should be stated concisely without discussion and should not normally contain any references. The same data should not be presented in figures and tables. Do not repeat all the data that is set out in the tables or figures in the text; emphasize or summarize only important observations.

Formatting tables

• **Any table should be able to old on a single page** and should be included at the end of the manuscript. Download sample of correctly formatted tables (Microsoft Word 2002-2003, *.DOC): **Table 1**, **Table 2**.

Formatting figures

• Formats: PNG, JPEG only. **MUST BE SUBMITTED AS SEPARATE FILES**, not embedded in the main manuscript. Submit the best quality possible

Files must be named with the three letter file extension appropriate to the file type (eg: .jpeg, .png). You will be asked to provide figure labels during the submission process. (The label is the small comment that usually goes with the figure. Example: **Figure 1:** Prevalence of diabetes in the study population aged 18 years and above. Findings of the TRICARE Diabetes Study, Uganda, 2006.)

If you use excel to generate your graph, avoid 3D, crowded axes, colored background, strong grid etc.. Use Tahoma font (size 10 maximum) for all items in your graphs (Title, legend, axes etc..). Expand your Excel graph to obtain a large image, copy and paste it in Paint (Microsoft Paint), crop any white border and save the image as PNG or JPEG. Loot at an acceptable **formatted Excel graph here**

Discussion - The Discussion should deal with the interpretation of the results and not recapitulate them. We encourage authors to write their Discussion in a structured way, as follows:a) statement of principal

findings; b) strengths and weaknesses of the study; c) strengths and weaknesses in relation to other studies; d) discussion of important differences in results; e) meaning of the study; f) unanswered questions and future research.

Conclusion - The conclusion should provide a brief summarize of the key findings, potential implications and the way forward.

Acknowledgements - Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study. The role of a medical writer must be included in the acknowledgements section, including their source(s) of funding. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements. Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section. Authors must describe the role of the funding body, if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Competing interest - Authors are responsible for recognizing and disclosing conflicts of interest that might bias their work. They should acknowledge in the manuscript all financial support for the work and other personal connections. Authors are required to complete a declaration of competing interests. All competing interests that are declared will be listed at the end of published articles. Where an author gives no competing interests, the listing will read 'The author(s) declare that they have no competing interests'. When completing your declaration, please consider the following questions:

Financial competing interests

- In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.
- Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the

publication of this manuscript, either now or in the future? If so, please specify

- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? If so, please specify.
- Do you have any other financial competing interests? If so, please specify. Non-financial competing interests

- Are there any non-financial competing interests (political, personal, religious, ideological, academic, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.
- If you are unsure as to whether you, or one your co-authors, has a competing interest please discuss it with the editorial office.

Authors' contributions - In order to give appropriate credit to each author of a paper, the individual contributions of authors to the manuscript should be specified in this section.

References - References must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends. Reference citations should not appear in titles or headings. Each reference must have an individual reference number. Please avoid excessive referencing. If automatic numbering systems are used, the reference numbers must be finalized and the bibliography must be fully formatted before submission. We encourage

authors to use a recent version of EndNote (version 5 and above) or Reference Manager when formatting their reference list, as this allows references to be automatically extracted. Examples of the PAMJ reference style are shown below. Please take care to follow the reference style precisely; references not in the correct style may be retyped, necessitating tedious proofreading.

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Authors names are separated by coma. Article title starts after the author name series, precedes by a dot and terminated by a dot. Journal abbreviation or name dot then follow, with year; volume number and in brakets issue number, then page numbers if applicable. The format is:

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A maximum of 1500 words in the main text (i.e. excluding abstract, references and legends) plus up to ten references and normally no more than two illustrations (tables or figures or one of each). Otherwise in the same format as full- length original papers (see above).

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A maximum of 5000 words in the main text (i.e. excluding abstract, references and legends) plus up to 100 references. Reviews are usually solicited, although unsolicited Reviews may be considered for publication. Prospective writers of Reviews should first consult the Editors

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Competing interests from are seek from authors and reviewers. Reviewers declare any competing interests and have to agree to open peer review. This implies that authors and reviewers agreed that if the

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Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in

parentheses in the Methods section.

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- K Morin, H Rakatansky, FA Riddick Jr, LJ Morse, JM O'Bannon 3rd, MS Goldrich, P Ray, M Weiss, RM Sade, MA Spillman: **Managing conflicts of interest in the conduct of clinical trials.** JAMA 2002, 287 :78-84
- CD DeAngelis, PB Fontanarosa, A Flanagin: **Reporting financial conflicts of interest and relationships between investigators and research sponsors.** JAMA 2001, 286 :89-9
- R Smith: **Beyond conflict of interest.** BMJ 1998, 317 :291-292
- R Smith: **Making progress with competing interests.** BMJ 2002, 325 :1375-1376

For all articles that include information or clinical photographs relating to individual patients, written and signed consent from each patient to publish must also be mailed or faxed to the editorial staff. The manuscript should also include a statement to this effect in the Acknowledgements section, as follows: "Written consent for publication was obtained from the patient or their relative."

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