Estimation of Causes of Death in Suburban Nepal Using Verbal Autopsy

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ABSTRACT

Background

Nepal is in the midst of a disease transition, including a rapid increase of non-communicable diseases. In order for health policy makers and planners to make informed programmatic and funding decisions, they need up to date and accurate data regarding cause of death throughout the country. Methods of improving cause of death reporting in Nepal are urgently required.

Objective

We sought to validate SmartVA-Analyze, an application which computer certifies verbal autopsies, to evaluate it as a method for collecting mortality data in Nepal.

Method

We conducted a medical record review of mortality cases at Dhulikhel Hospital, Kathmandu University Hospital. Cases with a verifiable underlying cause of death were used as gold standard reference cases. Verbal autopsies were conducted with caregivers of 48 gold standard cases.

Result

Of the 66 adult gold standard mortality cases reviewed, 76% were caused by cancer, cirrhosis, cardiovascular disease, COPD or injury. When assessing concordance between cause of death from verbal autopsy vs. gold standards, we found an overall agreement (Kappa) of 0.50. Kappa based on broader ICD-10 categories was 0.69. Cause-Specific Mortality Fraction Accuracy was 0.625, and disease specific measures of concordance varied widely, with sensitivities ranging from 0-100%.

Conclusion

Ongoing, countrywide mortality data collection is crucial for evidence-based priority setting in Nepal. Though not valid for all causes, we found SmartVA-Analyze to provide useful general cause of death data, particularly in settings where death certification is unavailable.

KEY WORDS

Cause of death, death certification, Nepal, SmartVA, verbal autopsy

INTRODUCTION

Nepal is currently experiencing a health transition, with an increase in chronic, non-communicable diseases (NCDs).[1-10] According to the institute for health metrics and evaluation (IHME), only one of the top five contributors to Nepal's burden of disease in 1990 was a non-communicable condition. By 2010, this rose to three.[2] The percentage of deaths related to NCDs (excluding injuries) in Nepal varies, with estimates ranging from 49.2% to 60%, up from 30.3% in 1990.[2] Although initial epidemiological studies have given us estimates of the changing mortality burden, data from Nepal are scarce and often unreliable, especially in rural areas with few health services.[4,6,11-14]

Nepal has an established vital registration system; however, it fails to capture most deaths and cannot provide accurate cause of death (COD) estimates.[14,15-18] In recent World Health Organization reports, Nepal has made available the number of deaths each year, but offered no information on the causes.[15] The limited COD data available typically comes from hospital death records, the weak vital registration system, small cross-sectional studies, or extrapolations of COD distribution patterns from other countries, none of which provide a comprehensive or accurate epidemiological picture.[6,13,19,20]

Without a well-functioning vital registration system or other population-wide epidemiological studies on mortality, decision-makers lack accurate and timely data to inform health policy and programming. One feasible and realistic alternative for gathering COD data is the Verbal Autopsy (VA) method, which helps determine probable COD in cases where no medical records or documented death certification exists.[21-23] VA is performed by interviewing a close caregiver of the deceased regarding the signs and symptoms that preceded the decedent's death.

The IHME has recently developed SmartVA-Analyze, an application that implements computer certification of verbal autopsies using the Tariff Method.[24-26] The Tariff Method has been shown to be equally or more effective at accurately identifying cause of death compared to paper-based physician-certified methods and other computer-certified methods in a multicenter validation study.[25-26] Conducting VAs electronically removes the need for physician certification, thus saving significant time and resources.

To address the great need for better mortality data in Nepal, we designed a study to conduct a pilot validation of the SmartVA-Analyze application using medical records and data from DH. Identifying an alternative, valid, and practically feasible method to document cause of death is crucial in order to bridge the current gap of inadequate mortality data in Nepal.

METHODS

This study was conducted under the umbrella of the Dhulikhel Heart Study at Dhulikhel Hospital, Kathmandu University Hospital.[27] The target population for our study included adult residents (18 years or older) of Dhulikhel town and the surrounding catchment region. Verbal autopsy participants were eligible if they had been a primary caregiver during the final illness of someone who deceased in the previous year (January 2014 – December 2014). If the family member died suddenly, the participant should have been a member of the same household as the deceased. VA participants were identified through the family contact section of deceased patients' hospital registration records. Participants were excluded if their deceased relative passed away less than two months prior to the interview, out of respect for the mourning period. Additionally, the interviewers of the VA questionnaires were recruited as participants to give us feedback on the challenges and barriers to conducting VA in Dhulikhel. A minimum sample size was not calculated while developing the methods for this study. Instead, we aimed to use all hospital cases available that met our study sample criteria.

Our primary study variable was the underlying COD of mortality cases at Dhulikhel Hospital, Kathmandu University Hospital in 2014. Gold standard underlying COD was determined by reviewing medical records and death certificates of mortality cases at Dhulikhel Hospital, Kathmandu University Hospital. Verbal autopsy COD was determined through VA interviews using the population health metrics research consortium's (PHMRC) shortened questionnaire, which we translated into the Nepali language. The questionnaire was implemented electronically on the open data kit (ODK) collect system on an android platform. Interview responses were run through the SmartVA-Analyze application, which electronically processes data using the Tariff Method and produces a COD estimate at both individual and population levels for 34 adult causes, 21 child causes, and 6 neonatal causes.

Mortality data from the hospital records were collected using a paper based format and later entered in Microsoft Excel 2011. VA data were first collected using Android tablets and later uploaded into a Microsoft Excel 2011 database. Qualitative data from post-interview forms were recorded and analyzed in Microsoft Word 2011.

The phases of data collection are described below.

Phase 1 – Gold standard case selection

We began by obtaining all mortality files and death certificates of patients who died at DH during 2014. Because physical autopsies were not conducted at DH, we selected our gold standard cases through a medical record review. DH forensics physicians were trained to implement a protocol for diagnosing COD using a set list of criteria for each disease.[26] Each patient's medical record and death certificate were comprehensively reviewed to estimate the

underlying COD. Using criteria from PHMRC, we determined the strength of evidence for each diagnosis.[26] Gold standard cases, or "Level 1", were defined as having the highest level of diagnostic certainty. "Level 2" cases were considered to have a high level of certainty, and "Level 3" were those without sufficient diagnostic evidence.

Phase 2 – Validation of cod from SmartVA against gold standard medical records

Prior to beginning the validation, we tested for face and content validity as well as a reliability test. For reliability testing, we conducted the questionnaire with a group of 17 participants. After one week, a different interviewer re-conducted the interviews with the same group of 17 participants. This process gave the interviewers a chance to practice the interview, helped to ensure that our questionnaire was reliable and consistent, and it pointed out areas of improvement before formal validation interviews began.

After initial testing and questionnaire adjustment, we began contacting the caregiver or relative who was linked to the medical records of all gold standard mortality cases identified in Phase 1. Interviewers conducted the VA questionnaires with all consenting and eligible caregivers/ relatives of the cases that could be located.

Phase 3 – Identifying implementation challenges of the SmartVA

Following each VA interview, the interviewer completed a brief form describing any reactions to or challenges presented by the interview.

Descriptive analysis was conducted on the demographic information collected regarding the VA participants' households. Statistics on the age, sex, and education level of the deceased individuals were enumerated.

Cohen's Kappa was used to provide an overall level of agreement between the SmartVA COD estimate and the gold standard COD from medical record review. To evaluate the accuracy of the tool at an individual cause level, sensitivity and specificity were calculated with STATA 13 software using data from the SmartVA-Analyze tool and medical records. Chance-Corrected Concordance (CCC) was calculated as an alternative measure of individual level performance. To address population-level performance, a Cause Specific Mortality Fraction (CSMF) and CSMF-Accuracy were calculated.[28]

Qualitative data from post-interview forms sought to explore: (1) challenges experienced during interview, (2) language and comprehension difficulties, (3) alertness and attentiveness of participant, and (4) physical or mental discomfort of the participant. The interviews were transcribed into Microsoft Word 2011 and analyzed using thematic analysis techniques.

This study received ethical approval from the Institutional Review Board at the University of Washington Human Subjects Division as well as the Institutional Review Committee at Kathmandu University School of Medical Sciences. Informed, written consent was received from each participant before beginning data collection.

RESULTS

Medical record review and gold standard cause of death assignment

A total of 107 adult deaths (at or above age 15) were identified at DH during 2014. We were able to locate the complete medical records of 77 adult mortality cases; the medical records of 28% of the 107 total cases were missing. Because of the high number of missing cases, we included an additional 8 cases from mid to late 2013, giving us a total number of 85 medical records to review. A recruitment diagram is provided in Figure 1 and basic demographic information of the mortality cases is listed in Table 1.

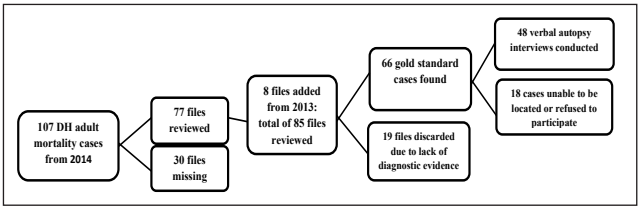

Figure 1. Recruitment flowchart for adult study participants

Table 1. Demographic characteristics of adult deaths

Characteristic	Number	%
Sex		(for all files reviewed)
Male	49	58%
Female	36	42%
Total	85	
Age		(for all files reviewed)
15-24	1	1%
25-44	17	20%
45-64	24	28%
65+	43	51%
Total	85	
Education		(for VA deaths only)
No education	15	31%
Primary School	22	46%
Secondary School	6	13%
Post Secondary	2	4%
Not listed	3	6%
Total	48	

Using PHMRC definitions, 33 cases were considered gold standard, or "Level 1" (highest level of certainty), another 33 cases were considered "Level 2", and 19 cases were "Level 3". Most of the Level 3 cases failed to meet gold standard criteria due to lack of sufficient diagnostic procedures performed or a lack of documentation within the patient

file. For example, not including radiology reports was noted in 53% of the Level 3 cases.

We recorded the COD data for the 66 Level 1 and Level 2 cases. A full distribution of these causes is displayed in Table 2. The COD data showed a considerably low percentage of communicable disease, with only 15% of deaths stemming from infectious diseases such as pneumonia, diarrhea, or tuberculosis. Non-communicable diseases accounted for the majority of deaths (85%), with 79% of deaths caused by cancer, cirrhosis, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), or injury.

Table 2. Number of gold standard causes of adult death, by age

Cause of death	Number of deaths				Total
	15-24 years	25-44 years	45-64 years	65+ years	
Communicable diseases					**10**
Pneumonia	0	1	2	5	**8**
Diarrhea	0	1	0	0	**1**
Tuberculosis	0	0	0	1	**1**
Noncommunicable diseases					**56**
Circulatory diseases					
Ischemic heart disease					
Acute MI	0	0	0	3	**3**
Congestive heart failure	0	0	0	1	**1**
Stroke	0	2	0	4	**6**
Respiratory diseases					
COPD	0	0	2	8	**10**
Digestive disorders					
Cirrhosis	0	8	4	1	**13**
Acute calculus cholecystitis	0	0	0	1	**1**
Appendicular perforation	1	0	0	0	**1**
Hernia - peritonitis	0	0	1	0	**1**
Neoplasms					
Lung cancer	0	0	0	3	**3**
Stomach cancer	0	0	1	2	**3**
Colon/colorectal cancer	0	1	2	0	**3**
Gallbladder cancer	0	0	1	0	**1**
Esophageal cancer	0	0	1	0	**1**
Cholangiocarcinoma	0	0	1	0	**1**
Endocrine/metabolic diseases					
Diabetes mellitus with renal failure	0	0	1	1	**2**
Alcohol withdrawal - hyponatremia	0	0	1	0	**1**
External causes					
Suicide	0	0	1	1	**2**
Falls	0	1	0	2	**2**

Verbal autopsy reliability testing

The 17 verbal autopsy reliability interviews conducted to prior to the validation interviews showed a variety of inconsistencies between the Round 1 and Round 2 participant responses, ranging from 2-20 inconsistent responses per participant. While some inconsistencies were minor, such as the specific age or date of death, some inconsistencies were of significant consequence. However, as expected, the inconsistencies became less frequent as interviewers gained more experience conducting the interviews. We found 50% fewer inconsistencies in the second half of reliability interviews compared to the first half.

We were able to conduct 48 VA interviews for validation out of the 66 gold standard adult cases identified (Level 1 and Level 2 cases). The primary reason for not including all 66 cases was the unavailability of caregiver contact information.

Because of overlapping signs and symptoms for many diseases, VA is generally not able to calculate COD with complete accuracy. We found this to be especially true for diagnosing some non-communicable diseases such as COPD, cirrhosis, ischemic heart disease (IHD), and stroke. Examples of misclassifications include:

- 3/5 misclassifications of cirrhosis were mistaken as "Other Infectious Diseases"
- 2/3 misclassifications of COPD were marked asthma
- 2/2 misclassifications of IHD were mistaken as "Other Cardiovascular Diseases"

For a complete table of the misclassifications, refer to Table 3.

The overall agreement (Cohen's Kappa) between the adult COD found from the VA and the gold standard COD was 0.50 when the specific disease (e.g. COPD, lung cancer, falls, stroke, etc.) was used to define COD. Kappa based on the broadest ICD-10 category (e.g. circulatory system, digestive system, neoplasms, etc.) was 0.69. Using criteria described by Landis and Koch,[29] our validation results were categorized with a "moderate" strength of agreement, or, if the broadest ICD-10 categories are used to define COD, a "substantial" strength of agreement.

In addition to Kappa, we also calculated sensitivity and specificity to compare the VA results with the gold standard. These values varied widely, with sensitivities ranging from 0% (e.g. stomach cancer) to 100% (e.g. falls). Table 4 provides a summary of these measures of accuracy for the most commonly found COD. The Chance-Corrected Concordance was calculated to be 0.522. Finally, we calculated CSMFs for population performance (see Figure 2), and a CSMF-Accuracy was calculated to be 0.625.[30]

Table 3. Misclassification matrix

Gold standard diagnosis	VA diagnosis													
	Pneumonia	COPD	IHD	Stroke	Other CVD	Diabetes	Cirrhosis	Cancer	Asthma	Diarrhea	Other infectious	Falls	Suicide	Others
Pneumonia	3									1				
COPD		5							2	1				
IHD			2		2									
Stroke	1			2						1				
Other CVD														
Diabetes						2								
Cirrhosis	1						4				3			1
Cancer					1		1	7						1
Asthm														
Diarrhea														
Other infectious														
Falls												3		
Suicide													1	
Others					2									1

Table 4. Validation characteristics of the most frequently found causes of adult death

Cause of death	N	Sensitivity	Specificity	PPV	NPV
Cancers*					
all cancers	10	20%	87%	28.6%	80.5%
Digestive diseases					
Cirrhosis	9	44.4%	97%	80%	88%
Respiratory diseases					
COPD	8	62.5%	100%	100%	93%
Pneumonia	4	75%	93%	50%	97.6%
Circulatory diseases					
Ischemic heart disease	4	50%	100%	100%	96%
Stroke	4	50%	100%	100%	96%
Accidents and injuries					
Falls	3	100%	100%	100%	100%

* Values for an exact cancer match are provided in the table; however, if we broaden the category to "any cancer", accuracy improves with a sensitivity of 70% and specificity of 100%. For example, under this definition, a gold standard diagnosis of colorectal cancer and a VA diagnosis of cervical cancer would be considered a match

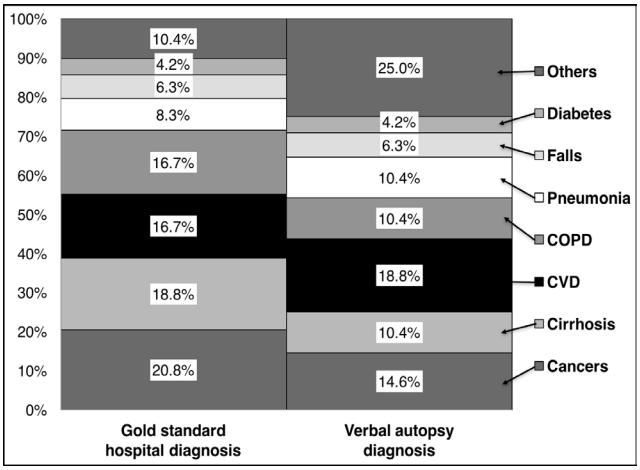

Figure 2. Cause specific mortality fractions (adult deaths)

Implementation challenges

Based on post interview surveys, we found the greatest challenge during VA interviews to be participant discomfort and distress. Recalling details of a family member's death was a difficult task for all participants, and we noted considerable discomfort in at least 15 participants. Interviewers reported events such as "the participant was being emotional, and I had to stop the questionnaire for awhile". Other comments included, "the participant got emotional and started crying" and "he was complaining about the quantity of questions and was not willing to tell anything regarding his wife's death." Interviews of a neonatal death were particularly challenging (emotionally) for the participant.

Another theme noted in the interviewers' reports was the participants' desire to receive more information regarding the death of their relative. Often, the participants left the hospital following their relative's death without a clear picture of what caused the death. Some falsely assumed that the VA interview would help bring clarity to their situation, and thus were disappointed not to receive information about the death. On multiple occasions, participants were skeptical about the interview, and did not fully comprehend what the purpose of the interview was. Though challenges existed, there were many positive reports as well and many welcoming, helpful participants who were happy to be interviewed and hospitable toward the interviewers.

DISCUSSION

This study demonstrated a high prevalence of non-communicable disease, especially circulatory diseases, respiratory diseases, digestive disorders, and cancer at DH. Nearly all of the infectious diseases stemmed from pneumonia. Our results showed a wide variation in the ability of SmartVA-Analyze to accurately identify individual COD. On a population-wide level, results showed CSMF Accuracy to be 0.625, with most misclassifications falling within the gold standard cause's broader ICD disease category. Our CSMF-Accuracy calculation is in relative agreement with the results of the original PHMRC validation study using the Tariff Method. With a median CSMF-Accuracy of 0.745, the PHMRC study result was higher than our result of 0.625.[25] This difference is possibly explained by a small sample size, cultural differences, and varying quality of medical records. The SmartVA is a new tool, and initial results from its application in the field are proving to be fairly consistent.

We observed a few concerns throughout the process of reviewing records that prevented us from using several mortality cases in the validation. The first concern was the substantial percentage of mortality cases with missing medical records. The hospital has a systematic process of submitting and storing medical files; however, storage space for medical records was lacking. Second, in our process to identify gold standard cases, we were impacted by missing or incomplete documentation. For example, many files had missing information (e.g. x-ray or other imaging tests). Other times, patient progress was not fully documented, such as missing notes on vital signs throughout the patient's admission. Finally, an international standardized death certificate was not in use nor was an ICD coding system, limiting both the quality and usability of medical records. With small improvements to records storage and the thoroughness of documentation, the medical records at DH could provide an excellent source of cause of death data for the country of Nepal.

There were also a few Nepali cultural factors that may have impacted our VA implementation. First, converting birth and death dates from the Bikram Sambat calendar used in Nepal to the western calendar was often complicated. Another cultural factor present was the emphasis placed on protecting the reputation of the deceased, especially in cases like suicide or tobacco-related deaths. For example, two of the three participants interviewed regarding a suicide case were uncooperative or exhibited "rude" behavior. Other times, participants did not give truthful information about the deceased's alcohol or tobacco habits.

Information from the post interview forms was used to evaluate the cultural suitability of implementing VA in Nepal. Though most participants found it distressing to discuss the death of their relative, nearly all were eventually able to offer details about the death and open up to the interviewer. In fact, some participants were very willing to talk about the death; it was perhaps a rare opportunity to be asked about their relative's death, and they were pleased to find someone who would listen. In this sense, the VA interview may have been helpful in the healing process of grieving family members.

Based on the results of this study, we recommend using VA in Nepal with the PHMRC VA instrument and SmartVA-Analyze software; although, we recommend with caution. We were able to obtain a general impression of the accuracy and feasibility of the tool. However, because of a small sample size originating from only one study site that did not include cases representing the full range of SmartVA causes of death, we were not able to provide rigorous evidence of the tool's validity or to perfectly duplicate the PHMRC validation study results.

SmartVA-Analyze should especially be used cautiously with certain causes of death that are more difficult to capture because of overlapping symptoms. In this study, specific types of cancer were difficult to capture with SmartVA-Analyze as well as some chronic diseases such as IHD, stroke, COPD, and liver diseases. Further research is necessary to find ways of differentiating the symptoms of these important diseases, especially between different types of cancers.

We identified multiple explanations for obtaining misclassifications throughout our study. On the interviewer side, errors can stem from poor delivery of the question, lack of thoroughness in explaining questions to the participant, trying to rush the interview, or even skipping questions for various reasons. On the participant side, explanations include recall errors and in some cases, cultural factors involving the protection of the deceased's reputation. Recall bias may be likely for at least three reasons. Firstly, relatives of a patient who died in a hospital may be better able to answer VA questions than a non-hospital mortality case, because they were exposed to more information regarding the deceased's symptoms and diagnoses. Secondly, even though we limited the time of interview to one year after the death of the patient, participants still may have simply forgotten the deceased's exact symptoms. Finally, issues of shock, stress, or guilt related to the death may cloud their recall ability. Other explanations for misclassification that we identified include divergent definitions of certain causes like sepsis, and cases with competing causes of death.

Overall, our team was satisfied with the automated format of the Android-based questionnaire. Although the purchase of tablets adds cost, we found that it ultimately saves substantial resources by removing the need for physician-review, which is required in non-data derived VA. In our study, interviewers had previously received certificates in the medical field; however, we concluded that medical training is not necessarily required for future interviewers. With thorough training on the meaning of and response options for each question, interviewers from many backgrounds could perform this role.

In Nepal, many people prefer to die in the comfort of their own homes. Ideally, Nepal should have a large-scale vital registration system that provides comprehensive and on-going COD data for all deaths, including home deaths. However, because Nepal does not currently have the capacity for such a system, VA may prove to be an effective method of tracking mortality in districts where death certification is currently unavailable, as long as the limitations of the results are understood. VA has had very limited use in Nepal, with most simply generating mortality data on a site-specific, single cause, such as neonatal mortality, birth asphyxia, under-five mortality, and maternal mortality.[31-39] There is great potential to scale up VA's use in Nepal, especially for all-cause mortality purposes.

Limitations

Our sample size was limited due to a minimal number of mortality cases in the hospital as well as certain cases being excluded due to missing records or incomplete documentation. Because our sample originated from only one study site and did not include cases representing all SmartVA causes of death, the results should be interpreted with caution, especially with certain causes of death that are more difficult to capture because of overlapping symptoms. Given that patients who die in a suburban hospital are not necessarily similar to populations who die at home or in rural areas, generalizability may be affected. In this study, specific types of cancer were difficult to capture with VA as well as some chronic diseases such as ischemic heart disease, stroke, COPD, and diseases of the liver. Further research is necessary to find ways of differentiating the symptoms of these important diseases, especially between different types of cancers.

CONCLUSION

To our knowledge, our study was the first attempt in Nepal to validate a verbal autopsy tool that assesses all-cause mortality, and one of the first attempts worldwide to validate the SmartVA-Analyze tool using the shortened version of the PHMRC questionnaire. Though our results showed that some inconsistencies exist when implementing SmartVA-Analyze in suburban Nepal, we found this tool useful in providing information on general population health trends and disease categories of primary concern. Scaling up VA implementation in Nepal can help provide decision-makers, donors, and health care providers with essential mortality data that can guide resource allocation and the development of relevant health policies and programming. With such a critical gap in Nepal's current mortality reporting capabilities, VA is likely one of the best immediate options for gathering COD data throughout the country.

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Potential Conflict of Interest:

Abraham D. Flaxman is the lead developer of SmartVA-Analyze, a freely available software tool for computer-certification of verbal autopsy interviews. As this software is given away free on the web (http://www.healthdata.org/verbal-autopsy/tools), this is a non-financial competing interest. No other potential competing interests exist.

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