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Usefulness of a smartphone application for the diagnosis of epilepsy: Validation study in high-income and rural low-income countries

Loretta Giuliano [a], Calogero Edoardo Cicero [a], Giancarlo Trimarchi [a], Valeria Todaro [a], Chiara Colli [a], Elizabeth Blanca Crespo Gómez [b], Alessandro Bartoloni [c], Vito Sofia [a], Victor Patterson [d], Mario Zappia [a], Alessandra Nicoletti [a,*]

[a] Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia", Neuroscience Section, University of Catania, Via S. Sofia 78, 95123 Catania, Italy
[b] Hospital Universitario Hernández Vera, Santa Cruz, Bolivia
[c] Department of Experimental and Clinical Medicine, Infectious and Tropical Diseases Unit, Careggi University and Hospital, Largo Brambilla, 3, 50134 Florence, Italy
[d] Faculty of Medicine, University of Khartoum, Sudan

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ABSTRACT

Introduction: In low- and middle-income countries (LMIC), the diagnosis of epilepsy should be made by Non-Physician Health Workers (NPHW) who are widely available in these settings. Recently a smartphone app (Epilepsy Diagnosis Aid) has been developed and validated to be used by NPHW, in order to confirm the diagnosis of epilepsy. The aim of our study was to perform a validation of the app in two different contexts: a hospital-based setting of a high-income country (HIC) and a population-based setting of the rural communities of a LMIC.
Material and methods: For the hospital-based setting, the app was administered to a sample of patients with epilepsy (PWE) and to a sample of subjects affected by syncope attending the epilepsy center of the University of Catania. For the population-based setting, performed in the rural communities of the Gran Chaco region in Bolivia, the app was administered by NPHW to a sample of PWE previously identified. Sensitivity and specificity were calculated for the diagnosis of epilepsy.
Results: In the hospital-setting, the app was administered to 100 PWE and 20 syncopes. A probability score > 80 showed a sensitivity of 76% (95%CI 66.4–84) and a specificity of 100% (95%CI 83.2–100) for the diagnosis of epilepsy; higher values were found for active epilepsy with tonic-clonic seizures. In the rural-setting, the app was administered to 38 PWE, giving a sensitivity of 92.1% (95%CI 78.6–98.3).
Conclusion: The app for epilepsy could represent a valuable instrument, which can be easily employed by trained NPHW to diagnose epilepsy in primary health-care settings of LMIC.

1. Introduction

There are over 50 million people with epilepsy worldwide, of whom three-quarters live in low- and middle-income countries (LMIC) [1]. In most of these countries more than 60% of people with epilepsy (PWE) do not have access to treatment for epilepsy and, if they do, they are often not able to adhere to the prescribed treatments [2]. The treatment gap in LMIC is higher in rural than in urban areas [2,3], and even if it can be due to different causes, in this setting PWE are often unable to access biomedical facilities for diagnosis due to the lack of neurologists as well as trained physicians [4]. Recently the World Health Organization (WHO) highlighted the need of the detection of epilepsy associated with convulsive seizures (EACS) as a priority in rural areas of LMIC, since it is associated with higher comorbidity, injury, stigma, and mortality than nonconvulsive epilepsy [5]. In this context, the WHO has wondered whether "*convulsive epilepsy can be diagnosed at first level care by a non-specialist health care provider in LMIC settings*" [6]. Indeed, EACS can be easily identified by trained Non-Physician Health Workers (NPHW) who are widely available in these settings, because of its clear clinical manifestations [7]. However, the burden of the confirmation of cases and initiation of treatment still relies on specialized medical staff.

In this regard, telemedicine and, in particular, smartphone applications (apps), might be potentially useful in epilepsy care, considering the rapid spread of smartphone technologies in the last decades also in LMIC [8]. Recently a smartphone app, the

* Corresponding author at: Department of Medical and Surgical Sciences and Advanced Technology "G.F. Ingrassia", Section of Neurosciences, University of Catania, Via Santa Sofia 78, 95123 Catania, Italy. Fax: +39 095 3782900.
E-mail address: anicolet@unict.it (A. Nicoletti).

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"*Epilepsy Diagnosis Aid*" app, has been developed, to be used by NPHW, in order to confirm the diagnosis of PWE in LMIC [9]. This app, developed [9] and then validated in India and Nepal [10], showed a good agreement level between the probability score of epilepsy obtained and the neurologists' diagnoses. Moreover, it was found to be time-efficient and easy to use also for computer-naïve NPHW with little training [10–12].

However, this app, designed to screen all types of epilepsy, has been validated only in LMIC where epilepsy was diagnosed just on clinical ground and classified as convulsive and nonconvulsive, leaving out a more specific epilepsy classification.

The aim of our study was to perform a formal validation of the "*Epilepsy Diagnosis Aid*" app in two different contexts. Firstly, we validated the app in a hospital-based setting of a High-Income Country (HIC), in a sample of patients for which an accurate epilepsy type and syndrome classification [13] was available in order to evaluate its sensitivity and specificity according to different epilepsy types and syndromes. Furthermore, we have also evaluated the sensitivity of the app in a population-based sample of PWE living in rural communities of the Gran Chaco region in Bolivia to evaluate the accuracy of the app in a Latin American Country (LAC).

2. Material and methods

2.1. Study setting and study population

2.1.1. Hospital-based validation

For the hospital-based setting, the app was administered to a sample of patients with diagnosis of epilepsy made according to the most recent criteria [13], consecutively ascertained between October 2018 and February 2020 at the epilepsy center of the University of Catania, Italy. During a routine follow-up visit, patients underwent a clinical evaluation, a video-EEG recording and the administration of the app. Their clinical, electroencephalographic and demographical data were then retrospectively obtained by reviewing medical records from the databases of the center. The app was administered by a medical student (GT) who was previously trained by a neurologist of the center (LG). The following clinical variables were taken into account: sex, age, age at diagnosis, intellectual disability, epilepsy type according to the most recent classification (focal, generalized, combined, unknown) [13], syndrome diagnosis when available [13], epilepsy etiology, diagnosis of epilepsy associated with convulsive seizures (EACS) [14], history of generalized tonic clonic seizures in the last 5 years, anti-seizure medications (ASMs) taken.

Moreover, the app has been administered to subjects with episodes of loss of consciousness evaluated in the same Neurology service, and for whom the diagnosis of syncope has been made after an extensive cardiologic evaluation according to the most recent guidelines [15].

2.1.2. Population-based validation

The population-based validation was performed in a sample of rural communities selected from the areas of Eiti and Gutierrez, located in the Cordillera Province in the Plurinational State of Bolivia. These areas are part of the Chaco region, which is a subtropical area of low forests and savannahs, inhabited by indigenous Guaraní people. They live in communities that often lack basic services such as running water or electricity, basing their economy on animal husbandry and agriculture. According to previous studies in this area, the prevalence of lifetime epilepsy (LTE) was 12.3/1000, while the lifetime prevalence of EACS was 7.2/1000 [3,16].

The *Epilepsy Diagnosis Aid* app was administered to PWE, who were previously identified during a population-based survey. Diagnosis of epilepsy was made only on clinical ground and confirmed by a neurologist according to the latest ILAE classification, but seizure type being the maximum level possible for diagnosis [13]. For those patients, the following variables were considered: sex, age, age at diagnosis, intellectual disability, diagnosis of epilepsy associated with convulsive seizures (EACS) [14], history of generalized tonic-clonic seizures in the last five and two years, ASMs taken. The app was administered by nursing students attending the last year of their course at the Tekove Katu School in Gutierrez and who received a specific two-day training by a local neurologist, over the April–November 2019 period. Overall the training lasted about six hours. During the first day of the training, the neurologist explained the use of the app, answered questions about epilepsy and seizures, and discussed each app question with the students; during the second day, the students practiced the use of the app by administering it to each other and experimenting with specific situations with the help of the instructor. At the end of the second day, another question and answer session has been held. The school is an integral part of the educational and health system of the Bolivian State with the main aim of training staff in public health among the Guaraní people and other indigenous inhabitants of the region in order to get an "intercultural medicine".

The study has been approved by the Ethics committee of the Bolivian Neurological Society. It was developed in accordance with the STARD guidelines (Supplementary table 1).

2.2. Diagnostic tool

We used a smartphone version of the app *Epilepsy Diagnosis Aid* (developed by NetProphets Cyberworks Pvt Ltd). This app is designed to be administered to subjects older than nine years of age. It gives the probability that an episode of altered consciousness is due to an epileptic seizure based on the answers to 13 questions, providing an interpretation of the probability score obtained. In particular, subjects who obtain scores ≥ 80 are considered as "having epilepsy" and those with scores < 31 as "not having epilepsy" with the rest classified as uncertain [12]. The questions can be divided into four variables "*before the episodes*" such as gender, age, predisposing factors, and presence of eye witnesses; eight variables "*during the episode*" such as change of color, body stiffness, arms shaking, tongue biting, urine incontinence, head deviation, eyes closed, ability to communicate; one variable "*after the episode*" as the presence of weakness on one side of the body. The app can be administered to a proxy responder, in the case of patients with intellectual disability.

The app is available in English, Spanish, Portuguese, Arabic, Hindi, and Marathi languages. In particular, the Spanish version has been created by a Bolivian native language translator with the help of a neurologist to be integrated into the app. Furthermore, before its use in the validation study, it was pretested in the field by a local anthropologist in order to evaluate the comprehension of different items. Similarly, before its use in Italy, the app has also been translated into Italian and pre-tested in a small sample of 10 patients with epilepsy attending the epilepsy outpatient of the University of Catania for the hospital-based validation.

2.3. Statistics

The records of the app were stored on the mobile phone and later uploaded to a secure server from which they have been downloaded for analysis as a .csv file. The other clinical variables of patients were then added to the original database. The patients' information was anonymized. Qualitative variables were described as percentages and quantitative variables as mean ± standard deviation (SD). Sensitivity, specificity, and their 95%CI were calculated considering all types of epilepsy and separately for EACS and active EACS as well as for each different epilepsy type and syndrome.

Statistical analysis was performed using STATA 16 software packages (version 16.0, College Station, TX).

3. Results

3.1. Hospital-based validation in HIC setting

The *"Epilepsy Diagnosis Aid"* app was administered to 100 PWE (50 females [50%]; mean age 38.1 ± 14.9 years) and 20 subjects with syncopes (16 females [80%]; mean age 45.5 ± 24.7 years) (Table 1).

Among PWE, the mean age at disease onset was 20.4 ± 19.3 years. The majority of them (46%) had a well-controlled epilepsy with absence of seizures in the last three months, while 36% of them reported five to ten seizures in the last three months. Thirty-four (34%) subjects had an anamnestic report of seizures in cluster; 14% of PWE had intellectual disability, and 8% a history of febrile seizures. We were able to classify epilepsy syndromes for all patients except for four (4%) among the generalized epilepsies: two were patients with only generalized tonic-clonic seizures (GTCS) and photosensitivity, two were defined as combined generalized and focal epilepsy. Moreover, for five (5%) we were unable to determine whether they were focal or generalized and were thus classified as unknown. All of these forms were characterized by GTCS.

Fifty-three (53%) presented at least one GTCS and 17 (32.1%) of them had had the last GTCS during the last five years (active EACS). Among focal epilepsies, 11 (16.4%) had convulsive seizures in the last five years. Regarding treatment, 84% of PWE were currently taking ASMs with a median number of drugs taken of two (range 1–4).

Among PWE, we obtained a mean epilepsy probability score of 80.4 ± 30.8, while mean score was 5.6 ± 8 in the group of patients without epilepsy. In particular, 76% of PWE were correctly identified by the app, reaching an epilepsy probability score ≥ 80; 12 (12%) were classified as borderline (cut-off 30–79) and 12 (12%) were incorrectly considered as not having epilepsy (score < 31). These latest 12 subjects, incorrectly classified by the app, had EACS in 58.3% (seven cases), but none of them had had GTCS in the last five years. The other five cases without EACS had focal epilepsy in two cases (one frontal lobe epilepsy and one nocturnal epilepsy) and generalized epilepsy in three cases (one juvenile myoclonic epilepsy and two epilepsy with absences). On the other hand, all 20 subjects with syncopes were correctly classified as nonepileptic (epilepsy probability score < 31). The characteristics of all false-negative subjects are reported in Table 2.

Considering all types of epilepsy, the app showed an overall sensitivity for the diagnosis of epilepsy of 76% (95%CI 66.4–84) and a specificity of 100% (95%CI 83.2–100) as shown in Table 3. When the analysis was restricted to EACS only, the sensitivity was of 77.4% (95%CI 63.8–87.7) and the specificity 100% (95%CI 83.2–100), while for epilepsy without GTCS sensitivity was 74.5% (95%CI 59.6%–86.1%). Nonetheless, the sensitivity of the app was of 100% (95%CI 79.4–100) and the specificity 100% (95%CI 83.2–100) when considering only active EACS (Table 3).

Sensitivity for the different epilepsy diagnoses is shown in Table 4. Overall, a sensitivity level higher than 70% was obtained for all types of epilepsy (generalized and focal) except for absence and juvenile myoclonic epilepsy for which a lower sensitivity was obtained, as shown in Table 4.

Considering the different items, the question with the highest level of sensitivity was *"Can they communicate?"* with the answer "no" having a sensitivity of 94.9% (95%CI 88.6% to 98.3%) while the question with the higher specificity level was *"Is there weakness on only one side?"*, considering positive answers, with 100% of specificity (95%CI 83.2–100) (Table 4). The values of accuracy of the single questions, when considering only EACS, are shown in Table 5.

3.2. Population-based validation in rural LMIC setting

The app was administered to 38 PWE (15 females [39.5%]; mean age of 29 ± 17.3 years). The mean age at disease onset was

Table 1
Demographic and clinical features of patients with epilepsy in the hospital-based and population-based settings.

	Hospital-based Validation (*N* = 100)	Population-based Validation (*N* = 38)
Sex (women)	50 (50%)	15 (39.5%)
Mean age (Mean ± SD, years)	38.1 ± 14.9	29 ± 17.3
Intellectual disability	14 (14%)	9 (23.7%)
Age at onset (Mean ± SD, years)	20.4 ± 19.3	14.7 ± 12.2
Epilepsy etiology		
Structural	44 (44%)	/
Genetic	29 (29%)	/
Unknown	27 (27%)	/
Generalized epilepsies	28 (28%)	/
Juvenile myoclonic epilepsy	9 (9%)	/
Epilepsy with absences	10 (10%)	/
Epilepsy and generalized tonic-clonic seizures alone	5 (5%)	
Other	5 (5%)	/
Focal epilepsies	67 (67%)	/
Temporal Lobe Epilepsy	28 (28%)	/
Frontal Lobe Epilepsy	22 (22%)	/
Other Focal Epilepsies	10 (10%)	/
Nocturnal Epilepsy	7 (7%)	/
Unknown epilepsy	5 (5%)	
Focal without bilateral diffusion	33 (33%)	3 (7.8%)
EACS	53 (53%)	35 (92.1%)
Active EACS	17 (17%)	33 (94.2%)
Nonconvulsive epilepsy	47 (47%)	5 (5.8%)
ASM treatment	84 (84%)	25 (65.8%)

Legend: SD, standard deviation; EACS, epilepsy associated with convulsive seizures: ASMs, anti-seizure medications.

Table 2
Characteristics of false-negative subjects in hospital-based and population-based validations.

	Hospital-based Validation (*N* = 24)	Population-based Validation (*N* = 3)
Sex (women)	19 (79.2%)	2 (66.7%)
Age (Mean ± SD, years)	39.4 ± 13.9	20.7 ± 3.2
Intellectual disability	3 (12.5%)	0
Age at onset (Mean ± SD, years)	15.9 ± 11.7	12 ± 6.1
Epilepsy etiology		
Structural	8 (33.3%)	/
Genetic	9 (37.5%)	/
Unknown	7 (29.2%)	/
Generalized epilepsies	9 (37.5%)	/
Juvenile myoclonic epilepsy	4 (16.7%)	/
Epilepsy with absences	4 (16.7%)	/
Epilepsy and generalized tonic-clonic seizures alone	1 (4.2%)	/
Focal epilepsies	15 (62.5%)	/
Temporal Lobe Epilepsy	7 (29.2%)	/
Frontal Lobe Epilepsy	5 (20.8%)	/
Other Focal Epilepsies	2 (8.3%)	/
Nocturnal Epilepsy	1 (4.2%)	/
EACS	12 (50%)	2 (66.7%)
Active EACS	0	2 (66.7%)
Nonconvulsive epilepsy	12 (50%)	1 (33.3%)
ASM treatment	12 (50%)	2 (66.7%)

Legend: SD, standard deviation; EACS, epilepsy associated with convulsive seizures: ASMs, anti-seizure medications.

Table 3
Values of accuracy of the app.

	Sensitivity% (95% CI)	Specificity% (95% CI)	TP	FP	TN	FN
Epilepsy*	76.0 (66.4–84)	100.0 (83.2–100)	76	0	20	24
EACS*	77.4 (63.8–88.7)	100.0 (83.2–100)	41	0	20	12
Active EACS*	100.0 (79.4–100)	100.0 (83.2–100)	17	0	20	0
Nonconvulsive*	74.5 (59.6–86.1)	22.6 (12.3–36.2)	35	0	20	12

Legend: CI, confidence intervals; TP, true positive; FP, false positive; TN, true negative; FN, false negative; EACS, epilepsy associated with convulsive seizures.
*Epilepsy probability score cut-off ≥ 80.

Table 4
Sensitivity values for different epilepsy types and etiologies.

	Sensitivity % (95% CI)
Epilepsy etiology	
Structural	81.8 (67.3–91.8)
Genetic	69 (49.2–84.7)
Unknown	74.1 (53.7–88.9)
Generalized epilepsies	
Juvenile myoclonic epilepsy	55.6 (21.2–86.3)
Epilepsy with absences	60 (26.2–87.8)
Epilepsy and generalized tonic-clonic seizures alone	88.9 (51.7–99.7)
Focal epilepsies	
Temporal Lobe Epilepsy	75 (55.1–89.3)
Frontal Lobe Epilepsy	77.3 (54.6–92.2)
Other Focal Epilepsies	80 (44.4–97.5)
Nocturnal Epilepsy	85.7 (42.1–99.6)
Unknown epilepsy	100 (47.8–100)

Legend: CI, confidence intervals.

14.7 ± 12.2 years. Thirty-five out of 38 patients were affected by EACS (92.1%) while three had seizures other than EACS (1 had atonic seizures and 2 had focal seizures with motor manifestations). Thirty-three out of 35 subjects (94.2%) had active EACS with seizures in the last five years, while 27 (77.1%) in the last two years. Among all patients, 25 (65.8%) were taking ASMs. Baseline characteristics are reported in Table 1.

The mean probability score for epilepsy among PWE enrolled in the rural setting was 93.6 ± 14.8.

Thirty-five out of 38 PWE were correctly identified by the app with a probability score higher than 80, giving a sensitivity value of 92.1% (95%CI 78.6–98.3). Among the three subjects uncorrectly identified by the app, one answered always "I don't know" to almost all the questions, giving a probability score of 61; one had 17 years and answered "No" to all questions since she had the last seizure at the age of 14, thus not remembering the episodes; one only reported stiffening and tongue biting, with a resulting score of 35. Features of false-negative subjects are reported in Table 2. For patients with EACS, the sensitivity level obtained by the app was of 94.3% (95%CI 80.8–99.3), while for active EACS it was 93.9% (95%CI 79.8–99.3).

The question with highest level of sensitivity was *"During the episode, can they communicate?"* (94.7%; 95%CI 82.2–99.4).

4. Discussion

Epilepsy is a treatable disease, but in rural LMIC, most people with epilepsy are not undergoing any treatment, often because they cannot access doctors. Indeed, in rural communities NPHW such as nurses and community health workers play a key role in providing medical care and social support and often they are the only health-care staff available to recognize epilepsy [17]. In this setting, in fact, neurologists are rarely available and general practitioners (GP) often move every year to different rural areas while nurses and NPHW are usually permanent members of the communities [7]. For this reason, the WHO promotes that trained nonspecialist health-care providers should be able to diagnose EACS in LMIC [17].

During the last decades, different validated screening tools have been developed to identify people possibly affected by EACS in rural areas [18–20]. These instruments, often consisting on a single screening question directed to the householder, have generally demonstrated a high sensitivity level and can be effectively administered by trained NPHW in order to quickly identify suspected cases of EACS at a community level. However, after the screening phase, NPHW in LMIC should be provided with efficient and easy tools to be used in order to correctly classify epilepsy and, whenever possible, starting a treatment. In this context, the *Epilepsy Diagnosis Aid* app has been specifically developed to help the NPHW confirm episodes of loss of consciousness as of epileptic nature or not with good accuracy [10]. The app was developed in English and firstly validated in Nepal [10] where a probability score > 80 showed a sensitivity of 92% and a specificity of 100% in correctly identifying PWE. On the other hand, a probability score < 31 showed a sensitivity of 100% and a specificity of 72% in correctly identifying subjects not having epilepsy. The high level of accuracy of the app was further confirmed in a subsequent study carried out in the same region [21]. Nonetheless, it should be noted that in these studies, epilepsy was diagnosed just on clinical ground and thus simply classified as convulsive or not convulsive seizures [21]. Moreover, except for few cases, the majority were affected by EACS and were active epilepsy cases. Indeed, in rural areas of LMIC, where EEG and neuroimaging are rarely available, diagnosis of epilepsy is commonly based on clinical ground and

Table 5
Values of accuracy of the different questions for all epilepsy types and for EACS only.

	All epilepsy types		EACS	
	Sensitivity % (95% CI)	Specificity % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
Is there a colour change to red or blue?	11.9 (5.9–20.8)	95 (75.1–99.9)	10 (2.8–23.7)	95 (75.1–99.9)
Is there stiffening?	67.7 (57.5–76.7)	94.4 (72.7–99.9)	75 (61–86)	94.4 (72.7–99.9)
Is there shaking?	67.7 (57.5–76.7)	83.3 (58.6–96.4)	75 (61–86)	83.3 (58.6–96.4)
Is the tongue ever bitten?	35.6 (29.7–50.1)	94.7 (74–99.9)	46.1 (32.2–60.5)	94.7 (74–99.9)
Is there ever incontinence of urine?	23.7 (15.7–33.4)	95 (75.1–99.9)	32.7 (20.3–47.1)	95 (75.1–99.9)
Does the head ever turn to right or left?	30.4 (20.5–41.7)	100 (81.5–100)	32.5 (18.6–49.1)	100 (81.5–100)
Are the eyes closed?	82 (72.4–89.4)	80 (56.3–94.3)	80.8 (66.7–90.8)	80 (56.3–94.3)
Can they communicate?	94.9 (88.6–98.3)	0 (0–16.8)	96.1 (86.8–99.5)	0 (0–16.8)
Is there weakness on only one side?	3.3 (0.7–9.3)	100 (83.2–100)	4 (0.5–13.7)	100 (83.2–100)

Legend: EACS, epilepsy associated with convulsive seizures; CI, confidence intervals.

EACS often represent the most common type of epilepsy reaching a frequency up to 90% [22]. Minor seizures such as absence or focal seizures without bilateral diffusion are, in fact, usually unrecognized and consequently underestimated.

In order to evaluate the sensitivity and specificity of the app for the different types of epilepsy, we validated the app in a hospital-based setting of a HIC. In particular, differently from previous validation studies, all patients in our hospital sample had undergone EEG and MRI and specific epilepsy types or syndrome diagnoses were available for the majority of them. Overall, for a probability score > 80, we obtained a high level of sensitivity and specificity when considering all types of epilepsy (76.0% and 100% respectively), even if sensitivity was slightly lower with respect to the estimates reported in Nepal. [21], Nonetheless, this finding can be explained by the lower proportion of patients with EACS (53%) included in our hospital-based sample. In fact, when the analysis was restricted to patients with a diagnosis of EACS, the sensitivity of the app increases, reaching values of 100% in patients with active EACS, estimate close to those reported in the previous validation studies [10]. Our hospital-based validation study also demonstrated a high level of sensitivity for almost all types of epilepsy including the focal ones for which sensitivity ranges from 72% to 86%. As expected, a lower level of sensitivity was reached for myoclonic and absence seizures (55.6% and 60%, respectively), which, being in a tertiary level epilepsy center of a hospital-based setting, may be the major seizure types of epileptic syndromes that usually are also characterized by the presence of GTCS. In fact, in patients with an adequate antiepileptic treatment, such as those followed in a tertiary hospital center, GTCS are usually well controlled.

Another important finding of our study was the very high level of specificity demonstrated by the app, with all subjects affected by syncope, thus classified as not having epilepsy and scoring < 31 at the app administration. This finding has certainly important consequences since, by excluding all subjects with diagnoses other than epilepsy, unnecessary and costly treatments can be avoided with positive health and economic implications. Furthermore, a possible clinical application of the app in a HIC could be its use especially in emergency rooms, where the diagnosis of epileptic seizures often turns out to be incorrect or, even worse, it can be missed in a high proportion of cases [23].

The second aim of our study was to evaluate the sensitivity of the epilepsy diagnosis app in a rural area of the Bolivian Chaco using a population-based design. Firstly, concerning the feasibility, the app was easily administered by the NPHW directly in the rural communities after a short training. We found a very high value of sensitivity for the whole sample (92.1%), thus confirming the high level of accuracy of the app when used by NPHW in rural LMIC [10]. In this setting, in fact our sensitivity overlaps with the estimates reported in Nepal probably due to the similar characteristics of the sample that also in this case was mainly represented by active EACS (92.1%). In this population of patients, the very good accuracy level demonstrated by the app is, therefore, of outstanding importance, since subjects with active EACS are the ones who need to be actively screened and diagnosed in order to start an adequate antiepileptic treatment, with the final aim of reducing the treatment gap, as highlighted by the WHO guidelines [17].

Our study has two important strengths. The recruitment of well-defined PWE after an extensive diagnostic process in the hospital-based sample allowed us to establish the accuracy for the different epilepsy types and syndromes. The second strength is related to the validation of the app in two different settings, a HIC hospital and a LMIC rural area. The high level of accuracy found in both samples, with similar values of sensitivity, especially for active EACS, demonstrates the high reliability of the app regardless of the study setting and design.

Certainly our study accounts for some limitations. First, concerning the validation in HIC, the number of PWE highly exceeds the number of subjects without epilepsy screened with the app. This is due to the hospital setting of our study represented by a tertiary epilepsy center of a HIC, where almost all the cases examined have a diagnosis of epilepsy, while all the other differential diagnoses are mainly managed at a primary care level, thus not referred to a specialized center. At any rate, the excellent result obtained with all patients without epilepsy identified as negative by the app, partly compensates for the small number of the sample. Furthermore, it should be noted that the diagnosis of syncope was achieved after an extensive evaluation performed by a cardiologist according to the most recent diagnostic criteria [15]. Moreover, all subjects had a diagnosis of syncope, differently from the previous validation study carried out in Nepal in which nonepileptic seizures were mainly psychogenic nonepileptic seizures [10]. Also in Nepal's study, the app correctly classified all the nonepileptic seizures leading to a specificity of 100% for diagnosing epilepsy. A further limit is related to the hospital-based case–control validation design that may have led to a sensitivity overestimate, due to the higher likelihood for the affected cases to be positive at screening [24].

Concerning the rural setting, we focused only on a small sample of patients previously identified as PWE, but we did not include patients without epilepsy, thus we were unable to estimate the number of false positives and true negatives in order to estimate the level of specificity. Furthermore, also in this case, we cannot exclude that sensitivity of the app could change among newly diagnosed PWE.

Nonetheless, our results confirm the belief that this epilepsy app could represent a valuable instrument, which can be easily employed by trained NPHW to diagnose epilepsy in primary health-care settings of LMIC, as recommended by the WHO [17].

The use of this app in LMIC has been integrated in a model of care incorporating the results of the app used by NPHW and a remote epilepsy specialist, through the use of telemedicine [21].

Indeed, integrating the use of this app in a more extensive model of care for PWE in LMIC could have an important health-care impact. After a screening of the population, which can be easily implemented by NPHW through the use of the existing validated tools [18–20,25], the confirmation of the diagnoses and the initiation of treatment can be made through a combined approach incorporating NPHW using the app and a remote epilepsy specialist, connecting the two by phone [21]. In fact, it has been demonstrated that this last part of the model can be safe, effective in obtaining seizures control, appreciated by patients, and time-effective [21].

However, in order to create such integrated system, more studies are needed, especially in other LMIC and possibly using a population-based design, including never diagnosed PWE, to prove the generalizability of this strategy and to analyze its cost-effectiveness to make its application feasible for the health-care systems of resource-poor countries.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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