Research article

Real-world evaluation of novel eye drop bottle sensors: Cloud-based AI support for eye drop adherence

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A B S T R A C T

Purpose: To understand real-world eye drop adherence among glaucoma patients and evaluate the performance of our proposed cloud-based support for eye drop adherence (CASEA).
Design: Prospective, observational case series.
Methods: Setting: The Department of Ophthalmology at Tsukazaki Hospital.
Patient or study population: Glaucoma patients treated at the hospital from May 2021 to September 2022, with 61 patients initially enrolled.
Intervention or observation procedures: Pharmacists guided eye drop administration before the study. Changes in bottle orientation were detected using an accelerometer attached to the container, and acceleration waveforms and date/time data were recorded. Patients visited the clinic during the 4th and 8th weeks to report their eye drop administration, and the data were uploaded to the cloud.
Main outcome measures: Two AI models (B-LSTM) were created to analyze the eye drop bottle movement time-series data for patients treating one or both eyes. The models were evaluated by comparing the true administration status with the AI model judgment.
Results: Four of the 61 study subjects dropped out. The remaining 57 patients achieved recall, precision, and accuracy values of 98.6 %, 98.6 %, and 95.9 %, respectively, for the two-eyes model and 95.8 %, 98.8 %, and 95.6 % for the one-eye model. Three low-accuracy participants (77.1 %, 71.0 %, and 81.0 %) improved to 100 %, 99.1 %, and 100 %, respectively, after undergoing an additional 8-week performance validation using an aid-type container designed to ensure that the bottle was fully inverted during instillation.
Conclusions: CASEA precisely monitored daily eye drop adherence and enhanced treatment efficacy by identifying patients with difficulty self-medicating. This system has the potential to improve glaucoma patient outcomes by supporting adherence.

1. Introduction

Glaucoma is a common cause of blindness later in life [1]. Eye drop therapy is the most widely indicated and mainstream glaucoma treatment used [2,3], as surgical treatment carries the risk of complications [4]. Patients must use eye drops for the rest of their lives to avoid developing glaucomatous vision loss [5]. There are many challenges to medication adherence among people with glaucoma. In one study, nearly half of the patients were reported to stop using their eye drops within the first six months after initiation [6]. Such poor adherence increases the risk of visual field damage [7,8]. Nevertheless, the percentage of patients who continue using eye drops for one year has been reported to be 40 % [9]. A major problem with managing eye drop adherence is the unreliability of patient self-reports. Even in daily clinical practice, when physicians inquire about a patient's eye drop status, there is a tendency for the patient

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to overreport their usage [10,11]. Furthermore, physicians' estimates of patient adherence are unreliable [11]. Several efforts have been made to monitor eye drop adherence using electronic devices that do not require patient reporting. One method monitors the opening and closing of the lid of a case that holds the eye drop bottle [12], another uses a thin electronic force sensor of the bottle to measure the pressure ejection during eye drop administration as an activation signal [13], and a third incorporates an accelerometer inside the eye drop bottle [14]. Another study introduced a sleeve designed to detect eye drop use by measuring fluid level [15]. Such electronic devices not only represent a simple approach to accurately monitoring adherence but also act as motivation to encourage eye drop use; this is known as the Hawthorne effect, when individuals are prone to modify their behavior in response to being observed, as in the case of a patient's perception of their eye drop medication status being monitored by medical professionals [16].

Deep learning, synonymous with modern artificial intelligence (AI), has made it possible to extract features from unstructured images, videos, and time-series waveforms for the first time [17]. In other words, deep learning technology can evaluate structured adherence information, such as whether an eye drop has been applied, and unstructured information, such as whether eye drop administration is performed well. A previous report showed that more than 15 % of glaucoma patients could not apply the drops properly [18]. We previously reported on an AI-based container-type prototype for administering eye drops for glaucoma therapy [19]. Here, we developed a second-generation container-type eye drop adherence measurement system that addresses issues identified by the previous prototype and aimed to evaluate the performance of this system (cloud-based AI support for eye drop adherence, CASEA) for practical use and for improving the effectiveness of patient treatment in the real world. We also designed this system to be further used as a support tool for pharmacists to provide patients with face-to-face eye drop education. We created AI models using bidirectional long short-term memory (B-LSTM), which has excellent characteristics for time-series waveform analysis [20,21]. Compared to the waveform imaging AI model we used in previous reports [19], this model provides a more efficient identification process and more accurate measures of eye drop application [21]. Our AI model for identifying eye drop motion was installed on a cloud server, and pharmacists uploaded the eye drop motion waveforms stored in the eye drop bottle sensor to a dedicated website to display patients' eye drop adherence status in a calendar on the website. The calendar display of the eye drop adherence status and a 3D reproduction of the eye drop application can be viewed on a PC monitor as an educational tool. In addition to a silicone universal-type container, we used a container with a complex plastic aid for patients with difficulty applying the eye drops as determined by the pharmacist during face-to-face instruction.

In this study, we conducted an experiment to demonstrate the use of CASEA among glaucoma patients and investigated its performance. At the same time, we measured the effectiveness of CASEA in identifying patients with poor eye drop administration. Additionally, we validated the performance after additional eye drop education and eye drop aids.

Visit	Eye dropping	Number of eye drops	Guidance of eye drop given by the pharmacist for use of eye drops
Day 1	Four weeks of eye-drops with sensors		(1) Accurately administer one drop in each eye. (2) Each drop should take less than 30 seconds to administer. (3) When dosing both eyes, after placing a drop in one eye, place one in the corresponding location in the other eye. (4) Point the eye-drop bottle straight down and hold it firmly downward.
Week 4	The same as above	Matching between patient report and CASEA identification by the pharmacist	Instructions by CASEA
Week 8		The same as above	Instructions by CASEA
Patients with relatively poor eye-drop movements were statistically extracted for additional verification.			
Additional Day 1	Four weeks of eye-drops with a supportive container		After explaining that the extracted patients had low-performance scores for the formal eye-drop motions, the pharmacist obtained consent to redo the verification with an eye-drop aid attachment.
Additional week 4	The same as above	Matching between patient report and CASEA identification by the pharmacist	Instructions by CASEA
Additional week 8		The same as above	Instructions by CASEA

Fig. 1. Flowchart of the study. The validation period for the main study and the additional investigation was eight weeks, with three face-to-face explanations and interviews conducted by the pharmacist, once on the first day and twice every four weeks. A conventional, universal eye drop bottle sensor was used in the main study, and an eye drop bottle sensor with an eye drop motion aid attachment was used in the additional study. CASEA: Cloud-based AI support for eye drop adherence.

2. Methods

2.1. Ethics

This study passed ethical review by the Ethics Committee of Tsukazaki Hospital (ethical approval number: 201022) and was conducted in accordance with the Declaration of Helsinki. Written consent was obtained from all patients in person.

2.2. Overall study structure

The present study on CASEA consisted of an eye drop bottle container with a sensor, AI models, and a cloud system. It included glaucoma patients treated from May 2021 to September 2022 at the Department of Ophthalmology at Tsukazaki Hospital. A pharmacist (K.N.) explained the purpose of the experiment to all patients and obtained informed consent. Then, after providing instructions on administering the eye drops, eye drop bottle sensors were given to patients who had provided support to participate in the study. The pharmacist, seated across from the patients, conducted face-to-face interviews in a dedicated interview space. After four weeks, the patients returned to Tsukazaki Hospital (first visit), and the waveform data stored in the eye drop bottle sensor were uploaded to a cloud server so that an AI model could evaluate eye drop bottle use. Face-to-face interviews by the pharmacist were conducted in the same style as previously described, with patients reporting their eye drop status and giving feedback on using CASEA. After another 4-week interval (56 days after the start of the experiment), the patients completed a second follow-up visit to Tsukazaki Hospital, in which the exact steps were completed. Face-to-face interviews by the pharmacist were again conducted in the same style. We determined which patients were significantly poorer during the main validation in administering eye drops. We gave them an additional validation period (4 weeks x 2, for eight weeks) of the same length as the primary validation and a container with an assistive device. Fig. 1 shows the study flowchart.

2.3. Participants

Patients with early glaucoma who regularly visited the general outpatient clinic at the Department of Ophthalmology of Tsukazaki Hospital and were using glaucoma eye drops were enrolled in this study. The exclusion criteria included scheduled eye surgery during the study period, dementia, and difficulty visiting the hospital. Patients who did not agree to participate in the study and patients who
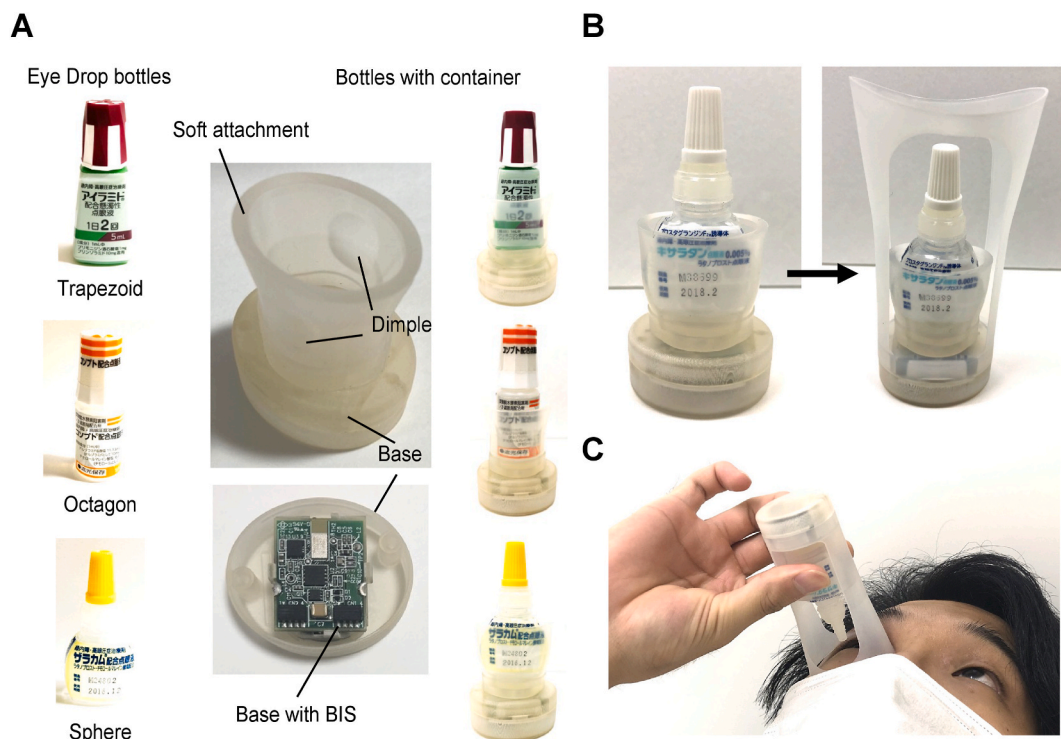

Fig. 2. Containers for cloud-based AI support for eye drop adherence (CASEA) and eye drop administration. A. The container is made of soft silicone and can accommodate eye drop bottles of various shapes. The battery-integrated sensor (BIS) is housed in the base, and both sides of the attachment have dimples that are approximately half the thickness of the floor to make the device easier to hold. B. Right: normal eye drop bottle container, left: eye drop bottle container equipped with the eye drop AI system. C. Eye drop administration with the eye drop aid.

were unable to point the tip of the eye drop bottle downwards as instructed by the pharmacist were also excluded.

2.4. Face-to-face instruction and interviews

Before patients began participating in this study, a pharmacist (K.N.) explained that an AI model would automatically detect eye drop bottle use from the movements of the eye drop bottle that were recorded by the sensor stored in the eye drop bottle container and that the results would be used in this study. At this point, the pharmacist (K.N.) also confirmed that when the tip of each eye drop bottle was pointed downwards, one of the motions in the standard set that the pharmacist taught the patients to perform, the AI detected this as the correct motion of the bottle for eye drop administration. The pharmacists also instructed the patients to report any times when they forgot to administer the drops during face-to-face interviews, which were conducted twice at four-week intervals, and that if there were any discrepancies between the patient's self-reports during the interviews and the AI judgments of eye drop bottle use, the pharmacists would determine the true bottle use after another face-to-face interview. During the interview, the pharmacists compared patients' reports with the status of eye drop administration determined by CASEA. They instructed them on administering the eye drops using 3D demonstrations by CASEA.

2.5. Configuration of the eye drop bottle sensor

The eye drop bottle sensor included an eye drop bottle (Fig. 2), a sensor circuit board with a battery holder (middle lower of Fig. 2A), an eye drop bottle container (middle upper of Fig. 2A), and a cord connected to a personal computer (PC) (Supplementary Fig. 1C). The container base was hollow to allow the installation of the sensor circuit board. A CR2032 lithium coin cell battery (225 mAh) (Panasonic, Tokyo, Japan) was used as the power source and was held in place with the attached integrated battery holder.

The electronic circuitry of the sensor circuit board consisted of a microcomputer unit (EYSHSHZWZ, Taiyo Yuden Co., Ltd., Tokyo, Japan), a 3-axis accelerometer (ADXL363, Analogue Devices Inc., MA, USA), and 64 megabytes of flash memory (MX 25R6435FZAIH0, Macronix Co., Ltd., Hsinchu, Taiwan). The microcomputer unit had a built-in real-time clock (RTC) function, allowing the time and eye drop movement data to be recorded to the flash memory of the sensor circuit board (Supplementary Fig. 1).

2.6. Eye drop bottle container

The silicone eye drop bottle container consisted of a base section (including a base cover) and an attachment section stabilizing the eye drop bottle(middle upper of Fig. 2A). This container was made of a hard polymethyl methacrylate oval base with a major diameter of 40 mm, a minor diameter of 35 mm, and a height of 20 mm, as well as a soft silicone (30 hardness on a type A durometer) attachment with an oval bottom with a major diameter of 27 mm and a minor diameter of 24 mm and a 30 mm-high conical shape that expanded to a major diameter of 32 mm and a minor diameter of 25 mm at the aperture. The weight of the eye drop bottle container alone was 13.6
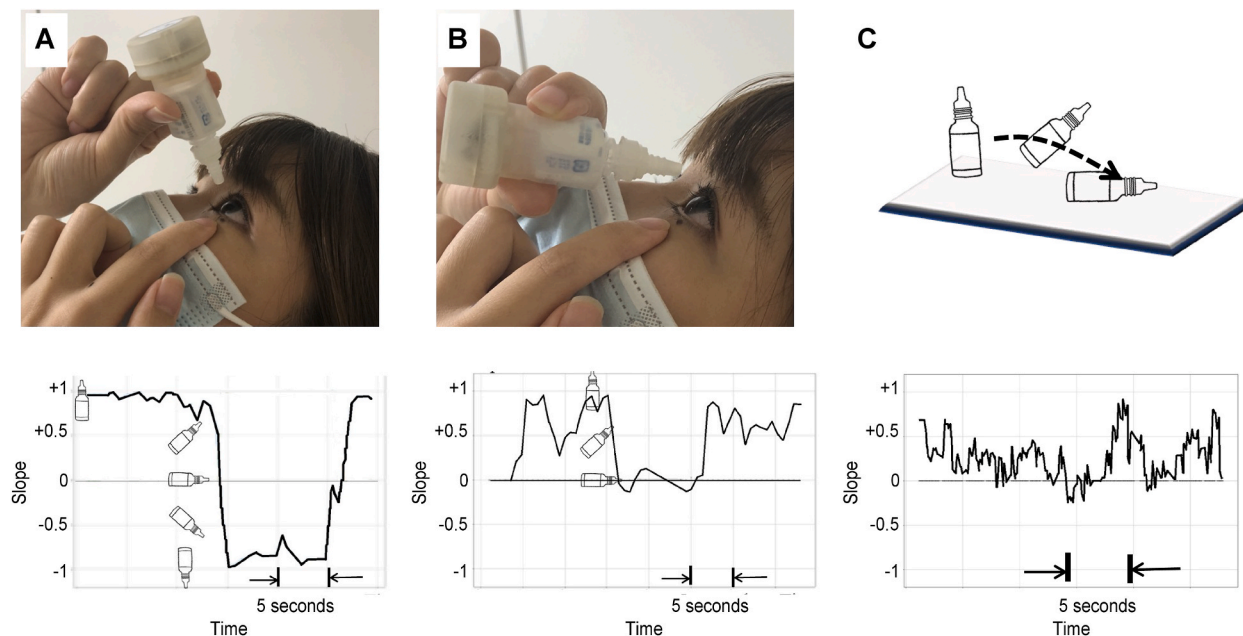

Fig. 3. AI authentication performance of three outliers in normal and aid containers.
An additional 8-week validation using the aid container was conducted for the three outliers among the 57 study participants. The recall, which indicates the eye-drop motion judgment performance, reached 100 % for all three participants using the aid container.

g, which increased to 20.2 g when including the battery and sensor substrate. The flexible attachment could be adapted to 5-ml capacity sensor bottles of various shapes; we confirmed that it could be used with ten differently shaped glaucoma eye drop bottles approved in Japan (Both ends of Fig. 2A).

Another eye drop bottle container was created similarly but had an attached polymethyl methacrylate eye drop aid. This aid-type container had a maximum height of 96 mm, an opening diameter of 50 mm along the long axis, and an opening diameter of 40 mm along the short axis.

2.7. Accelerometer data recording, storage, and AI model

Our previous report [21] details the preprocessing of the accelerometer data and the AI model (Supplementary Fig. 2). Two AI models using B-LSTM were created for binocular eye drops and single-eye movements, and multiple reprocessing was performed accordingly. We trained AI models on 2954 correct waveforms for the standard eye drop motion with the tip of the bottle pointing straight down (this eyedrop procedure is recommended to simultaneously achieve therapeutic effects and prevent infections/side effects due to the bottle touching the skin around the eye) and 3213 incorrect waveforms for various eye drop motions, such as falling or movement within a shoulder bag. Fig. 3 illustrates various waveforms captured from the sensor during ophthalmic motion. Fig. 3A shows a typical correct waveform when the eye drop is properly administered. Fig. 3B represents a typical boundary waveform, where the bottle tip remains horizontal, indicative of a borderline correct application. Fig. 3C depicts a typical incorrect waveform, which occurs when the bottle is merely rolled over, rather than being used to administer an eye drop. The system determined that an eye drop motion was performed when the time for which the confidence value exceeded 50 % for the binocular and monocular AI models was longer than 4 and 2 s, respectively.

2.8. Battery

At the beginning of the experiment, the pharmacist placed a new battery in the container. We used the same battery unless data acquisition stopped. We recorded the frequency of battery replacement.

2.9. Web system and data transfer

For CASEA, the two AI models' computations were performed on a proprietary web service on the Google Cloud Compute Engine VM (GCP) (Google LLC, CA, USA), and the result was displayed in the browser. The web services used included PHP: Hypertext Preprocessor version 7.2 for the server script, HTML5, and JavaScript for the browser display, Fullcalender (jQuery, MIT license, USA) for the calendar display, and 3D Three.js (Ricardo Cabello) for the 3D display. The calendar showed the results of the AI analysis, the period during which the eye drop experiment occurred, the times at which and how often the eye drops were administered, and the percentage of eye drop applications within the eye drop period as the adherence rate (Supplementary Fig. 3). In addition, a function allowed the reproduction of the eye drop motion waveforms obtained by the three-axis accelerator in a 3D animation (Supplementary Fig. 4). The 3D animation is designed to behave based on the inclination values calculated from the acceleration sensor.

2.10. Eye drop administration judgments

The pharmacist (K.N.) made the final decisions (pharmacist judgments) regarding the administration of eye drops by comparing the patients' self-reports of forgotten eye drop administration and the results output by CASEA (system judgments). The pharmacist adopted the system judgment if the patients' self-reports and the system's conclusions were consistent. In cases of discrepancy between the AI results and the patient reports, the pharmacist judged whether a "section," a waveform that survived the preprocessing [21], was extracted within 30 min before or after the patient's reported eye drop administration time. If there was no "section" in the hour before or after the patient's reported time, the pharmacist judged that the eye drops were not administered and that the patient had mistakenly reported doing so, even if there was no report of forgetting to administer the eye drops. When an eye drop behavior waveform "section" was extracted from the preprocessing results, the pharmacist judged that the eye drops had been applied even if the system judgment indicated a non-eye drop motion.

2.11. Performance evaluation

The recall, precision, and accuracy of CASEA were calculated as performance indices when eye drops were administered to both eyes and when eye drops were administered to one eye. The recall was defined as true positives (TPs)/(TPs + false negatives (FNs)), precision as TPs/(TPs + false positives (FPs)), and accuracy as (TPs + TNs)/(TPs + TNs + FPs + FNs). For the entire cohort, outlier patients were defined as those whose accuracy was below the 25th percentile minus 1.5 x the interquartile range.

2.12. Validation of the use of eye drop aids for outlier patients in the CASEA trial

For patients whose accuracy fell below the threshold defined above, an additional 4-week CASEA trial was conducted using an eye drop bottle container (supportive container) with an attached polymethyl methacrylate eye drop aid (Fig. 2B and C). Fig. 2B shows the difference between the normal and supportive containers. Fig. 2C illustrates how to use the supportive container. This aid forced the

direction of the tip of the eye drop bottle downwards when patients placed this aid in contact with the periocular area. The steps described above were then repeated in the same manner.

2.13. Ophthalmic data

Patients' mean deviation (MD) values from a Humphrey Field Analyser (HFA) (ZEISS, Oberkochen, Germany) were obtained from medical records within six months before the start of this study or measured at the beginning of this study or during either follow-up visit (4 or 8 weeks). Intraocular pressure (IOP) measurements were taken with an iCare Pro tonometer (ICARE FINLAND OY, Vantaa, Finland) at the start of eye drop therapy (initial IOP), at the first visit (1st visit IOP), and at the second visit (2nd visit IOP). The percentage of IOP reduction was determined as the mean of two values: (initial IOP - 1st visit IOP)/initial IOP and (initial IOP - 2nd visit IOP)/initial IOP. In addition, the IOP values at the start of the experiment and the first and second visits were compared using separate paired t-tests. For patients prescribed eye drops in both eyes, the IOP of the right eye was the subject of study.

2.14. Statistical analyses

Comparative analyses were conducted using the paired-t test. All statistical calculations, including basic statistical measures, were performed using JMP 16.2.0 (SAS Institute, USA).

3. Results

3.1. Included and excluded patients

A total of 61 glaucoma patients gave consent to participate in the current study. Of these, four dropped out after the pharmacist's initial explanation: two were uncomfortable with being supervised, and two demonstrated poor eye drop administration behavior with the eye drop bottle containers. The latter patients could not point the tip of the eye drop bottle downwards during the pharmacist's eye drop instruction.

3.2. Patient demographics and characteristics

There were no dropouts among the 57 enrolled patients during the study period. Thirty-one and 26 patients required eye drops in both eyes and one eye, respectively. Table 1 shows eye drop implementation rates, mean deviation (MD) values measured by the Humphrey Field Analyser (HFA), and intraocular pressure (IOP) data. Eye drop implementation rates were over 95 %; the mean MD values of the two groups were approximately −6 dB (dB), and IOP values were significantly lower than those measured at the initial session. None of the cases required battery replacement during this period.

3.3. Types of eye drops used in this study

Supplementary Table 1 shows the types of eye drops used in this study and the percentages of patients who utilized them. Seven and six types of glaucoma eye drops were prescribed to patients who used eye drops in both eyes and one eye, respectively. A total of nine different prescriptions were used in this study.

3.4. Performance of B-LSTM models

Recall, precision, and accuracy were 98.6 %, 98.6 %, and 95.9 %, respectively, among the 31 bilateral eye drop patients and 95.8 %, 98.8 %, and 95.6 % among the 26 patients who used eye drops for one eye.
These results are detailed in Table 2.
In addition, representative true positive (TP), true negative (TN), false positive (FP), and false negative (FN) waveforms for a patient who required Xalatan eye drops in both eyes are shown in Supplementary Fig. 5.

3.5. Extraction of low-performing patients for whom AI model identification was an outlier

Supplementary Fig. 6 shows a scatter plot of the recall and precision rates for the 31 patients who used eye drops in both eyes and

Table 1
Patient demographics and characteristics in our study for assessing the real-world practicality of CASEA.

Types	Eyes	Age	Female	HFA MD	Lowering IOP rate
Binocular drops	31	73.4 (8.2)	16 (51.6 %)	−6.3 (6.5) dB	13.4(18.8)%[a,b]
One eye drop	26	73.5 (8.4)	18 (69.2 %)	−5.9 (5.2) dB	10.2 (28.2) %[c,d]

The values are represented as the means (SDs). [a, b, c, d] indicate significantly decreased IOP values in the first and second sessions compared to the initial values according to paired t tests. [a]; $p < 0.0001$, [b]; $p = 0.0024$, [c]; $p = 0.0079$, [d]; $p = 0.0045$.

Table 2
System performance in discriminating eye drop administration movements for both eyes and one eye.

Binocular model	System prediction			
	Drop	Non-drop		
Pharmacist judgement (n = 31)				
Drop	2102	68	2170	Recall 98.6 %
Non-drop	30	176	206	
	2132	244	2376	
	Precision 98.6 %	Accuracy 95.9 %		
Pharmacist judgement (n = 26)				
Drop	1610	71	1681	Recall 95.8 %
Non-drop	20	342	362	
	1630	413	2043	
	Precision 98.8 %	Accuracy 95.6 %		

In the present study, the pharmacist's judgement was considered the true value and was determined by matching the patient reports of forgetting to administer the eye drops with the system estimates. The system prediction included the AI model judgements and the judgements.

the 26 patients who used eye drops in only one eye. The accuracy threshold for determining outliers was 86.3 % for patients using drops in both eyes and 85.6 % for patients using drops in one eye. The accuracies of one (3.2 %) patient in the both-eye group and two patients (8 %) in the single-eye group were below the relevant thresholds. The accuracy was 77.1 % for the outlier patients who administered eye drops to both eyes and 81.0 % and 71.0 % for the outlier patients who administered eye drops to one eye.

3.6. Accuracy improved in the three outlier cases when the eye drop applicator was used

In an eight-week additional study period, two of the three patients with below-threshold accuracies reached 100 % accuracy, while that of the remaining patients reached 99.1 %. All patients achieved 100 % recall, as shown in Fig. 4. Fig. 5 shows representative FP and TP waveforms. For all three patients, the waveform slope during the eye drop action remained near zero when using the normal container, regardless of whether the AI's judgment resulted in a false positive (Fig. 5A, D, and 5G) or true positive (Fig. 5B, E, and 5H). These cases represented borderline scenarios for the AI. However, when the aid container was utilized, the waveform during the eye drop action significantly dipped below zero for all instances (Fig. 5C, F, and 5I), providing a clear and easily distinguishable waveform pattern that facilitated more accurate AI differentiation. The slope is defined by the accelerations in the X, Y, and Z directions (aX, aY, and aZ, respectively) as follows:
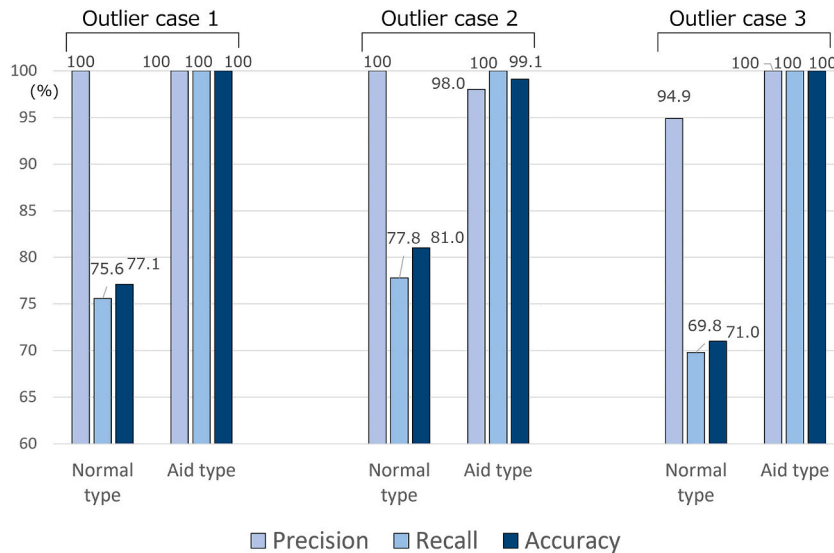

Fig. 4. Waveforms obtained by the sensor during various motions. A. In a typical correct eye drop motion, the orientation of the eye drop bottle tip drops sharply from the maximum value (+1), representing an upright orientation, to the minimum value (−1), representing an inverted orientation. Our AI models learned this type of waveform as the correct waveform. B. In an incorrect eye drop motion, where the tip of the bottle remains horizontal, the data stabilizes at a slope of approximately zero, indicating a horizontal orientation. C. For irregular behaviors, such as the eye drop bottle tipping over, the slope value rarely falls below zero and fluctuates in small increments in the positive range. Our AI models learned this type of waveform as an incorrect waveform.
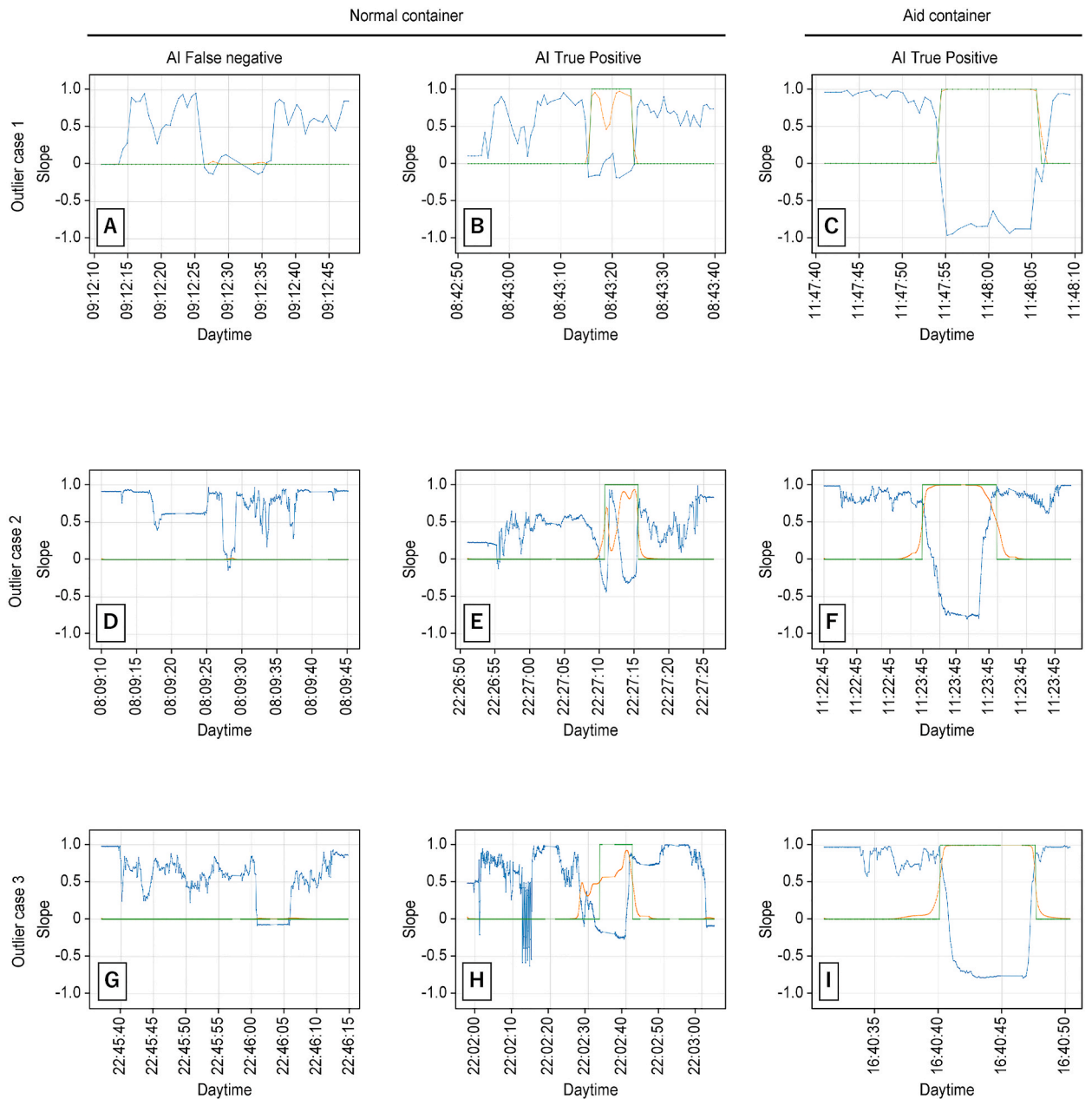
Fig. 5. Representative false positive and true positive AI judgment waveforms for a normal container-type eye drop bottle sensor and an actual, true favorable AI judgment waveform for the aid-type bottle sensor, all recorded from the three outlier patients.

Outlier patient 1: 64-year-old female, precision 75.2 %, MD value R-4.18, L-3.38 dB, Cosopt eye drops twice/day, mean IOP reduction 12.5 (10.8 %)%. Outlier patient 2: 69-year-old female, precision 77.8 %, MD, R-0.96 dB, Xalatan eye drops in the right eye once/day, mean IOP reduction 13.6 (6.4) %. Outlier case 3: 74-year-old female, precision 69.8 %, MD, L-16.1 dB, Tapcom eye drops in the left eye once/day, mean IOP reduction rate 9.1 (0) %. Blue line: Waveform obtained by the sensor (−1 for the whole downward position, 1 for the full upward position). Orange line: AI model value (confidence) (1 for eye drop movement, 0 for no eye drop movement). Green line: AI model discrimination label (1 for eye drop movement, 0 for no eye drop movement). In all three cases, the lowest point of the eye drop waveform slope was approximately 0 when a normal container was used, and the pitch was significantly less than 0 when a container offering technical aid was used.

$$arctan\left(\frac{a_z}{\sqrt{a_x{}^2 + \alpha y^2}}\right)$$

This slope is then normalized to a range between −1 and 1 by dividing it by π/2. The range of the slope is from −90° (when the Z-axis points directly upward) to 90° (when the Z-axis points directly downward); a slope of 0° indicates that the Z-axis is perfectly horizontal.

4. Discussion

In this study, we showed that the proposed container-type eye drop bottle sensor had good performance in monitoring clinical glaucoma patients, that the device could help detect patients who had difficulty with eye drops, and that patient adherence could be improved with an aid. The system did not require patients to perform tasks other than eye drop administration, and no battery replacement was necessary during the entire 8-week study period. In addition, AI models were used to evaluate data that reflected the effective administration of eye drops to one or both eyes, and the system was able to fit various shapes of eye drop bottles flexibly; nine types of glaucoma eye drops were used without any problems. Furthermore, we demonstrated the implementation of the entire system in the cloud. The advantage of deploying the system in the cloud is that pharmacists at different facilities can continue to manage eye drop adherence information, even when prescription refill patterns do not allow prescribing facilities to be identified in advance. The experiment showed that the system can objectively and automatically determine the status of eye drop use with high accuracy, precision, and recall.

The accuracy of CASEA was sufficient, indicating that it could be used clinically for patients with glaucoma. It has been reported that the average number of eye drops prescribed to patients with open-angle glaucoma is 1.74 per administration. Once-daily pro-pylene glycol (PG) drops and twice-daily beta blockers are the most common types prescribed [22]. If we assume that the average number of eye drops administered per day is 2, the total number of eye drops administered per month can be estimated as $2 \times 30 = 60$. If we apply the 96.9 % eye drop application rate for glaucoma patients in this study, we can assume that $60 \times 95.6\ \% = 58$ eye drops enter the eye per month, of which $58 \times 0.986 = 57$ would be identified by the current system given a recall of 98.6 % and only one drop would be missed. Compared to the patient self-reporting currently used in the clinic, which has been shown to lead to a 20 % rate of overreporting, the proposed system can lead to a more accurate assessment of eye drop therapy adherence.

Previous studies have identified many necessary motor skills, including aiming, pushing on the eye drop bottle, aiming while pushing on the bottle, and avoiding blinking, for successful eye drop application [23]. In this study, we identified three patients (3/57 = 5.3 %) who were classified by the AI tool as unable to perform the standard eye drop actions even after the pharmacist's instruction on using eye drops. The recall rate for all three patients at the end of the initial eight weeks was less than 80 %, indicating a large discrepancy between the standard recommended eye drop actions learned by our AI and those performed by the patients. In a previous report, a study of recorded patient eye drop motions showed that 17 % of the patients using 2.5-ml bottles and 25 % of patients using 15-ml bottles failed to perform the correct eye drop motion [18], which was notably higher than the recall rate of 5.4 % in our study using 5-ml eye drop bottles. This may be partly due to the improvement in eye drop movements with prior eye drop instruction from the pharmacist, but it may also be because our patients were mainly early glaucoma patients with an average HFA MD of approxi-mately −6 dB (dB); manipulating the eye drop bottle is known to become difficult for patients in later stages of glaucoma [18,23]. To help the outlier patients in the current study correctly administer the eye drops, we used an eye drop applicator attachment to help the patients perform the correct eye drop movements; after an additional eight weeks, we found that the recall rates improved to 100 % for all three patients. There have been multiple reports on the effectiveness of eye drop applicator attachments, suggesting that they play a role in improving the performance of electronic devices that have difficulty coping with atypical eye drop movements [24,25]. The possibility that our system, with its aid, could produce considerable clinical advances for patients who cannot apply eye drops well is a topic for future research.

Our system uses a state-of-the-art deep learning model specialized for time-series data to extract the features of time-series waveforms, which are difficult to structure. We believe, theoretically, its accuracy is high. On the one hand, the fundamental su-pervised nature of deep learning should be considered in interpreting this study's findings. From a statistical perspective, there is a 95 % accuracy performance limit in cases where discriminative boundary examples exist [26]. When the eye drop applicator was used to assist the patients in moving the eye drop bottles downwards, the AI judged that this was indeed an eye drop action, indicating the potential of this system as a tool for teaching eye drop administration to patients who cannot perform standard eye drop actions. On the other hand, a better ability to detect eye drop movements, even when those movements are not standard, is required for monitoring, and additional sensor technologies (gyroscopic, temperature, pressure, etc.) should be addressed in future studies.

Unlike our previous study, we did not use communication systems such as Wi-Fi in this study. The primary reason is that we do not believe that self-management is the best way to improve eye drop adherence. Face-to-face patient education has been reported to be more effective than telephone instruction or watching instructional videos [27,28]. It is difficult for patients with difficulty admin-istering eye drops to perform additional work to self-manage their administration, even if it involves only launching an app. We thought CASEA, which puts no extra burden on patients, would be the best way to improve eye drop adherence. The second reason is the issue of battery life: a 90 mA h battery in a combined Bluetooth and smartphone system is reported to last four weeks [13]. Regarding how much battery life is needed, an academic website for glaucoma patients states that the optimal interval between visits is 3–12 months [29]. In other words, the battery life must be at least three months to avoid needing replacement between visits; otherwise, a recharging system must be incorporated into the device, or the patient must replace the battery. The Hawthorne effect for

eye drop guidance and physician explanation is said to last only for a short period immediately after the visit [16], and the additional burden of battery replacement becomes an adherence barrier during long intervals between visits, defeating the purpose of the system. The issue of battery duration is a bottleneck for many future technologies. Ideally, a compact battery that does not need to be replaced for more than a year is needed [30].

There are several limitations in this study. Firstly, a significant limitation was the reliance on patient self-reports for actual eye drop adherence rather than a more reliable method such as video surveillance or in-lab validation. The gold standard we utilized - questioning of the patient by the pharmacist - has significant limitations. No in-lab work has correlated true positive and false positive use events with video-recorded laboratory settings to the waveforms. However, instructions at the beginning of this study emphasized that the movements of the patient's eye drops would be constantly monitored, and we did not think it was necessary to match the judgment of the AI in this study with patient self-reports that are often inaccurate in daily clinical practice [11]. If the patient-reported eye drop adherence is indeed overstated in our study, as is the case in daily clinical practice, the actual performance of the system is likely to be better than that shown by the current results since the cases that were counted as FNs by the AI models would be TNs. Second, there is no certainty as to whether the eye drops penetrated the eye, which has been noted as a limitation for both electronic devices and doctors. In our system, eye drop motions identified by the AI are standard eye drop actions. This means our method doesn't work well when the way of eyedropper is not directed straight downward. This is because we included only standard eye drop motions in the reference training data for deep learning. Patients who cannot perform that standard way should use the aid container. It is hypothesized that the corneal drop rate is very high when the bottle tip is directed straight down, especially when the aid container is used, but this point also needs to be confirmed in the future. Additionally, the container-type device we presented makes it explicit that patients are being supervised, potentially inducing a Hawthorne effect. Moreover, it is possible that the so-called white coat effect, which causes patients to want to be perceived positively by their doctors, resulted in intentional fake eye drop movements [31]. As seen in our study, The risk of being monitored may be uncomfortable and worsen adherence. Devices introduced nearly 40 years ago that hid an electronic system inside the eye drop bottle without the patient noticing had a considerable advantage in limiting the Hawthorne effect and the discomfort of being monitored [14]. This device is not yet available, but we believe that the older, yet innovative, idea of incorporating an adherence function into the eye drop bottle itself is ideal for managing eye drop adherence Finally, this was a short-term study conducted at a single hospital. Future long-term studies at multiple hospitals are needed to determine whether the same accuracy can be maintained in glaucoma patients who require a wide variety of lifelong drug treatments.

5. Conclusion

CASEA, a cloud-based system, is designed to facilitate multicenter studies. We assume it will enable future studies to investigate different glaucoma clinical adherence effects, such as increased IOP reduction rates, decreased dropout rates, and reduced residual medicine use. CASEA has the potential to achieve an objective and automatic understanding of eye drop adherence without depending on patient self-reporting. When objective eye drop status by CASEA is used as primary data for routine clinical practice, we believe that physicians can perform more precise and logical decision-making in glaucoma practice, especially in identifying surgical indications.

Financial disclosure

Data sharing

All data relevant to the study are included in this article.

Data availability

Data underpinning the findings presented in this study are not deposited in a publicly available repository. Instead, the relevant datasets are included within the article and its supplementary materials, or are referenced appropriately within the text.

CRediT authorship contribution statement

Hitoshi Tabuchi: Writing – review & editing, Writing – original draft, Conceptualization. **Kazuaki Nishimura:** Conceptualization. **Masahiro Akada:** Writing – review & editing, Writing – original draft, Conceptualization. **Tomohiro Ishikami:** Writing – review & editing. **Tomoki Shirakami:** Data curation. **Naotake Kamiura:** Formal analysis. **Yoshiaki Kiuchi:** Conceptualization.

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.

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34167.

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