

Article

Portable RGB-D Camera-Based System for Assessing Gait Impairment Progression in ATTRv Amyloidosis

Maria do Carmo Vilas-Boas ^{1,2} , Ana Patrícia Rocha ³ , Hugo Miguel Pereira Choupina ¹ , Márcio Neves Cardoso ², José Maria Fernandes ³ , Teresa Coelho ² and João Paulo Silva Cunha ^{1,*}

¹ Faculty of Engineering (FEUP), Institute for Systems Engineering and Computers—Technology and Science (INESC TEC), University of Porto, 4200-391 Porto, Portugal

² Unidade Corino de Andrade, Hospital Santo António, Centro Hospitalar do Porto, 4099-001 Porto, Portugal

³ Department of Electronics, Telecommunications and Informatics, Institute of Electronics and Informatics Engineering of Aveiro (IEETA), University of Aveiro, 3810-193 Aveiro, Portugal

* Correspondence: jpcunha@inesctec.pt

Abstract: Hereditary Amyloidosis associated with variant Transthyretin (ATTRv Amyloidosis) is a progressive and highly disabling neurological disorder that affects gait. Quantitative motion analysis is useful for assessing motor function, including gait, in diseases affecting movement. A single markerless RGB-D camera enables 3D full-body motion capture in a less expensive and intrusive, and more portable way than multi-camera marker-based systems. In this study, we examine whether a gait analysis system based on an RGB-D camera can be used to detect significant changes in the gait of ATTRv amyloidosis patients over time, when compared with a 12-camera system. We acquired 3D data provided by both systems from six ATTRv amyloidosis patients, while performing a simple gait task, once (T0) and 18 months later (T1). A direct comparison of systems has already been conducted. In this work, however, for each patient, we investigated if the RGB-D camera system detects statistically significant differences between the two different acquisitions in a similar way to the reference system, and whether it is reliable to use during patients' follow-up. The obtained results show that the differences detected between T0 and T1 for both systems follow the same tendency for 65% of the spatiotemporal gait parameters, and for 38% of the kinematic parameters (38%). The most reliable parameters were: stride duration/length, gait speed (and its variability), and arm/foot swing velocity, all with an almost perfect strength of agreement.

Keywords: gait analysis; Kinect; neurological disease; movement quantification; RGB-D camera; ATTRv amyloidosis



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1. Introduction

Hereditary Amyloidosis associated with variant Transthyretin (ATTRv Amyloidosis) is a rare, highly disabling, and inherently progressive neurologic disease. It is caused by an autosomal dominant genetic mutation in which Valine, located in position 30 of the TTR protein, is replaced by Methionine (V30M) [1]. The peripheral nervous system is especially affected by this disease, specifically the large myelinated as well as small non-myelinated fibers. This disorder is a nerve length-dependent symmetric polyneuropathy associated with autonomic dysfunction, which may lead to death within a decade from onset if left untreated [1–3].

In Portugal and Japan, the disease is usually reported as beginning in the third, fourth, or fifth decade of life; onset occurs typically later in patients from other geographical areas [4]. Its prevalence in northern Portugal (Póvoa de Varzim and Vila do Conde) was estimated to be 176.01/100,000 adult inhabitants in 2016 [5], representing the largest worldwide cluster of individuals with this condition. In Portugal, cumulative disease risk in individuals with the V30M mutation is estimated to be 80% by the age of 50 and 91% by the age of 70, whereas the risk in French heterozygotes is 14% by the age of 50 and 50% by

the age of 70 [6]. In Sweden, the penetrance is lower at 11% by the age of 50 and 36% by the age of 70, only reaching 52% prevalence by the age of 80 [7].

ATTRv Amyloidosis typically begins with the loss of temperature and pain sensations and hyperesthesia of the feet, in a slow progression of sensorimotor and autonomic neuropathy [3,4]. Afterward, sensory disturbances spread from the foot soles to the insteps, ankles, lower legs, knees, and thighs in a length-dependent manner. With further progression, motor deficits develop in the feet and progress in a proximal direction as well as in a length-dependent manner. By the time sensory neuropathy progresses to the level of the knees, the hands usually also become affected. In the late stage of the disease, sensory loss, muscle atrophy, and weakness of the extremities show a glove and stocking distribution (the name usually given to the symptom distribution in the areas covered by gloves or stockings). Foot drop and disability of the hands and fingers are also common symptoms of motor neuropathy. The disease can be classified into the following three stages: (I)—sensory polyneuropathy, (II)—progressive walking disability, and (III)—wheelchair-bound or bedridden [8].

Regarding treatment options, orthotopic liver transplantation was the first implemented approach (1990s) that succeeded in slowing disease progression [9,10]. In 2007, oral disease-modifying treatment became available for daily intake and has demonstrated long-term efficacy, although the deterioration of both clinical and neurophysiological domains was reported after 2 years of drug intake for some patients [11,12]. Other treatment options are under development [4,13,14]; however, challenges in clinical assessment remain due to the disease's rareness and a consequent lack of thorough knowledge, clinical heterogeneity, incomplete natural history, and uncertain treatment effectiveness [15]. Because treatment options in ATTRv amyloidosis are most beneficial at an early stage of the disease [4,10,16,17], the development and improvement of tools for objective measurements is of great importance [18].

ATTRv amyloidosis epidemiologic knowledge has expanded over the past years [19]. As in other neurologic diseases, motor polyneuropathy in ATTRv amyloidosis is monitored using serial nerve conduction studies that measure how fast an electrical impulse moves through the nerves, to identify nerve damages. Yet, movement is still analyzed using mostly subjective methods—gait evaluation is solely based on observation and clinical interrogatory—despite these being perceived as insufficient by the clinical community and lacking precision for identifying early-stage or subtle changes [20,21]. Recently, Vita et al., in a study with 20 ATTRv amyloidosis patients (aged 49 to 78), described the ability to use the 6-Minute Walk Test (6MWT) as a tool to monitor ATTRv amyloidosis patients, as it showed a good correlation with FAP and PND (Polyneuropathy Disability) scores [22]. Nonetheless, to our knowledge, there is no study on patients' gait progression.

Despite the variability of gait among subjects, there is an identifiable “normal pattern” [23]. Locomotion pathology produces abnormalities to this pattern, which in ATTRv amyloidosis patients was reported to be similar to the pattern of diabetic polyneuropathy patients. These “irregularities” may be identified, at some point, by visual observation [2,24,25]. The importance of a quantitative gait analysis tool lies in the possibility of measuring and/or detecting those abnormalities as soon as possible—even before being visible to the eyes—to help improve patients' diagnosis and treatment [20]. Abnormal gait may also be studied to develop occupational therapy strategies for improving work safety and life quality, thereby extending the period of active life of patients with highly disabling diseases such as ATTRv amyloidosis.

Until recently, complete full-body studies involving patients with gait impairments were only possible in dedicated laboratories, using specific and sophisticated equipment, based on multiple inertial sensors, such as accelerometers [26], or multiple infrared cameras that record the 3D movement of retro-reflective markers. The latter are placed on the patient's body using a specific configuration according to the research goal. These systems offer high precision and usability in biomechanics—often considered as the gold standard in this field—and may be combined with third-party equipment (e.g., force plates, EMG) [23,27]. However, they are usually expensive and restrictive for the majority of the population and clinical professionals.

Nowadays, new methods and tools are being developed to replace complex apparatus with smaller, more portable, less expensive, and less intrusive vision-based systems that rely on RGB-D cameras. A single RGB D camera, such as the Microsoft Kinect, provides color and depth image sequences, as well as 3D body joint position data, without requiring the placement of any sensor or marker on the subject's body.

Wearable sensors have also been widely used for gait analysis in different contexts [28]. However, they have the major disadvantage of having to be attached to the body, and are therefore intrusive for the patients. The use of only one or two wearable sensors can reduce their intrusiveness; however, fewer sensors can only offer limited information. To obtain full-body data, several sensors need to be attached to the different parts of the body, which can not only be complex and time-consuming to set up, but also quite uncomfortable and may restrict the movements of the patient. In this situation, markerless RGB-D cameras have the advantage of providing 3D body joint data related to the whole body in a minimally invasive way for patients, making them more suitable for use in clinical environments. Although an RGB-D camera cannot be used to continuously monitor a patient, as is possible with wearable devices, it is suitable for the scenario considered in this work, i.e., the support of clinicians during follow-up appointments with patients at the hospital.

1.1. Related Work

The Kinect's ability to assess 3D motion has been reported in the literature for healthy [29–39] and impaired [40–47] populations. Mentiplay et al. validated the Kinect v2 tool for gait assessment (30 healthy subjects), reporting that the studied spatiotemporal gait parameters had a consistent and excellent relative agreement; however, the kinematic parameters showed poor results [36]. Pfister et al. evaluated the gait of 20 subjects while walking and jogging at three velocities on a treadmill and assessed the validity of the Kinect when compared to a reference system [30]. Conclusions of this study included the poor performance of the system when assessing hip angular displacement, as well as a general under-estimation of joint flexion and over-estimation of joint extension. Otte et al. performed sensor validation for ranges of motions, torso sway, movement velocities, and cadence during sitting, standing, and walking activities [39]. They evaluated 19 healthy subjects and the joint movement signals showed moderate to excellent agreement, with noisier ankles and feet signals. As for clinical parameters, most of them showed good to excellent agreement. They concluded that the Kinect v2 can be used as a reliable and valid clinical measurement tool.

In studies with patients suffering from neurologic diseases, Galna et al. studied the agreement between the Kinect and a reference system for clinically relevant movements in Parkinson's disease, concluding that the Kinect tool can accurately measure timing and gross spatial parameters, but does not present the same spatial accuracy for smaller movements, such as hand clasping [43]. Behrens et al. [44,45] and Grobelny et al. [40] studied the use of Kinect v1 for supporting the gait assessment of patients with multiple sclerosis.

Our group carried out two studies that explored the possibility of using a Kinect for distinguishing between Parkinson's disease patients and healthy controls based on their gait [46,47]. Furthermore, we performed a study on gait analysis using a Kinect (version 2) involving ATTRv amyloidosis patients and healthy subjects [48]. In this study, we found that several gait parameters have the potential to be used to distinguish between ATTRv amyloidosis mutation carriers (with and without symptoms) and control subjects, and thus can be used to support ATTRv amyloidosis diagnosis and/or stage distinction.

We also carried out studies on the validity and/or reliability of the Kinect against a reference motion capture system, with a healthy population (N = 20) [49] and ATTRv amyloidosis patients (N = 6) [50]. The results achieved in both situations showed that a single Kinect can be used to obtain several spatiotemporal measures with excellent agreement with the reference system. This can be useful for supporting clinical evaluations during the 6MWT. Overall, results were better for spatiotemporal than for kinematic parameters.

A preliminary study on the ability of the Kinect to assess changes in the gait of ATTRv amyloidosis patients during their clinical follow-up was also performed by our group [51]. We carried out a quantitative gait analysis for six patients at two different moments in time (with an 18-month interval), which included the computation of thirteen gait parameters for each analysis and patient. Overall, we found that the Kinect can potentially be used for the defined aim based mostly on the considered spatiotemporal parameters.

In addition to the studies described above, there are reports of experiments using more than one Kinect v2 for gait analysis [31,32]. However, as we intend to find a suitable yet simple approach to use in a clinical ward, these contributions are out of the scope of this work.

1.2. Contributions

Our main contribution is studying the possibility of using an RGB-D camera-based system, which is an affordable, portable, and non-intrusive system, as a tool for supporting clinical gait assessment during follow-up of ATTRV amyloidosis patients, as an alternative to more expensive, time-consuming, and intrusive reference systems (as the Qualisys Motion Capture reference system), as well as to the present approach used in clinical practice (observation by the physician).

In contrast with studies that evaluate the Kinect's validity for gait analysis and/or its reliability in a short time interval (1 to 7 days) [29,30,36,39,41–44,52], our aim was to explore if the Kinect can be used for gait assessment over a longer period of time (in this case, 18 months), closer to the typical interval between consecutive clinical follow-up appointments. Despite the known limitations of RGB-D sensors for this task, especially for measuring angular parameters, we pursue the hypothesis that their systematic measurement errors do not have a large impact when analyzing gait variation over time for a given patient.

The present study includes the computation of the inter-rater agreement between the two systems (RGB camera and reference), based on the results regarding the presence or not of a significant difference between the two moments of assessment. To the best of our knowledge, besides our previous preliminary work, there is no similar study involving a ATTRV amyloidosis population.

We analyzed the gait of six ATTRv amyloidosis patients with a varying degree of gait impairment and heterogeneous disease progression, using the following two systems simultaneously: a reference motion capture system (multi-camera marker-based Qualisys system) and our gait analysis system based on a single RGB-D camera (Kinect v2) [53]. The gait analysis results included twenty-three gait parameters computed for each gait cycle and system. The analysis was performed twice (T0 and T1) for each patient, with an 18-month interval.

To assess the ability of our RGB-D camera-based system to detect significant changes in the patients' gait over time, we firstly investigated whether there was a statistically significant difference between T0 and T1, for each parameter, subject, and system. We then verified if our Kinect-based system was able to detect an actual significant or non-significant difference (Qualisys used as the ground truth) and, based on those results for both systems, we determined the inter-rater agreement for different sets of parameters, considering all subjects. This differs from typical validation studies that compare the systems directly and measure the error between them as shown in [49].

2. Materials and Methods

2.1. Subjects

We carried out an experiment at LABIOME (Porto Biomechanics Laboratory) where data were acquired once (T0) and then a year and a half later (T1) from 6 ATTRV amyloidosis patients (4 male and 2 female). The experiment was approved by the Ethics Committee of the Hospital Santo António (Centro Hospitalar Universitário do Porto, Porto, Portugal) and

complied with the Declaration of Helsinki. All patients provided their written informed consent.

The patients were being followed at Unidade Corino de Andrade (Centro Hospitalar Universitário do Porto) in an external consultation. Their demographic data, as well as clinical condition and progression information, are presented in Table 1. The only exclusion criterion was the presence of comorbidities.

Table 1. Demographics and clinical data for each patient that participated in the experiment.

Patient	Gender	Height (m)	Weight, T0 (kg)	Age, T0 (years)	BMI, T0 (kg/m ²)	BMI Variation (kg/m ² , T1–T0)	Years of Disease Progression, T0	Years Since Diagnosis, T0
P1	M	1.72	72.0	34	24.34	0.0	10	9
P2	M	1.73	58.5	33	19.55	1.5	9	8
P3	F	1.68	63.8	48	22.60	0.6	5	2
P4	M	1.82	99.3	45	29.98	0.0	8	6
P5	F	1.48	61.5	54	28.08	−1.4	18	17
P6	M	1.71	53.0	52	18.13	0.9	13	13

All participants were patients with the V30M mutation, but with different gait impairment degrees. They all had pain, thermal and tactile anesthesia, as well as reduced proprioception. They also presented some degree of motor deficit at the lower limbs. One patient had no strength deficit but had difficulty walking on heels, while the others lacked dorsiflexion from 4/5 to 0/5 (Medical Research Council Scale [54]) and plantar flexion from 4/5 to 1/5. All patients had a normal knee segmental force (5/5) at both T0 and T1. Overall, patients presented sensory ataxia and steppage gait with different instability and movement coordination degrees during stride. Steppage gait is characterized by the loss of dorsiflexion, consequent foot drop and high lifting of the leg. Visually, patients spread the legs to improve balance, exaggerate knee and hip flexion and are often observed “throwing” the feet forward, thereby improving ground clearance. They presented, therefore, very heterogeneous gait, although the clinical perception is that all alterations resulted from the sensory-motor polyneuropathy caused by the disease. The clinical evolution observed in each patient between T0 and T1 is described in Table 2.

Table 2. Clinical evolution of the ATTRV amyloidosis patients evaluated based on the Medical Research Council (MRC) Scale (0 is the worst condition and 5 the best). The PND (Polyneuropathy Disability) and ATTRV amyloidosis scores are also indicated (the values were the same at T0 and T1). PND score (0: no impairment, I: sensory disturbances but preserved walking capability, II: impaired walking capability but ability to walk without a stick or crutches, III a: walking only with the help of one stick or crutch, III b: walking with the help of two sticks or crutches, IV: confined to a wheelchair or bedridden); TTR-FAP score (I—sensory polyneuropathy, II—progressive walking disability, and III—wheelchair-bound or bedridden).

Patient	Clinical Condition at T0	Clinical Condition at T1	PND Score	TTR-FAP Score
P1	Dorsiflexion deficit (4)	Dorsiflexion deficit (4–)	II	I
P2	Dorsiflexion (0), plantar flexion (1), high steppage	Dorsiflexion (0), plantar flexion (0), knee flexion (4–), high steppage	II	I
P3	Difficulty walking on heels only	Difficulty walking on heels only & weakness at the toes	I	I
P4	Dorsiflexion (0), plantar flexion (3), steppage	Dorsiflexion (0), plantar flexion (3), steppage	II	I
P5	Dorsiflexion (4), plantar flexion (4), very low steppage	Dorsiflexion (3), plantar flexion (4), steppage	II	I
P6	Dorsiflexion (2), plantar flexion (1), steppage	Dorsiflexion (0), plantar flexion (1), steppage	II	I

Regarding treatment, three patients had been taking medication (tafamidis) for 10 months (P3), 3 years (P2), and 6 years (P1). One patient was enrolled in a different clinical trial for

not responding to tafamidis. Two patients were subjected to a liver transplant 8 (P6) and 12 (P5) years before the first analysis (T0). Patients suffered no evolution regarding PND and TTR-FAP scores from T0 to T1 (see scores in Table 2).

2.2. Experimental Setup and Protocol

The setup for the experiment included a reference motion capture system (Qualisys) and a single RGB-D camera (second version of the Kinect—Kinect v2), as depicted in [50]. The RGB-D camera was mounted on a tripod at a height of 1 m with a tilt angle of -5 degrees and placed in front of the participant. The tilt angle was chosen to maximize the practical depth range (i.e., the range for which the camera is able to track all body joints), which was around 2.9 m (1.5 m to 4.4 m) for the used configuration.

The Qualisys system included twelve infrared cameras and twenty-nine retro-reflective markers attached to the patient's body as illustrated in Figure 1. Patients were asked to wear tight-fitting shorts and upper body garments to facilitate the proper placement of the markers.

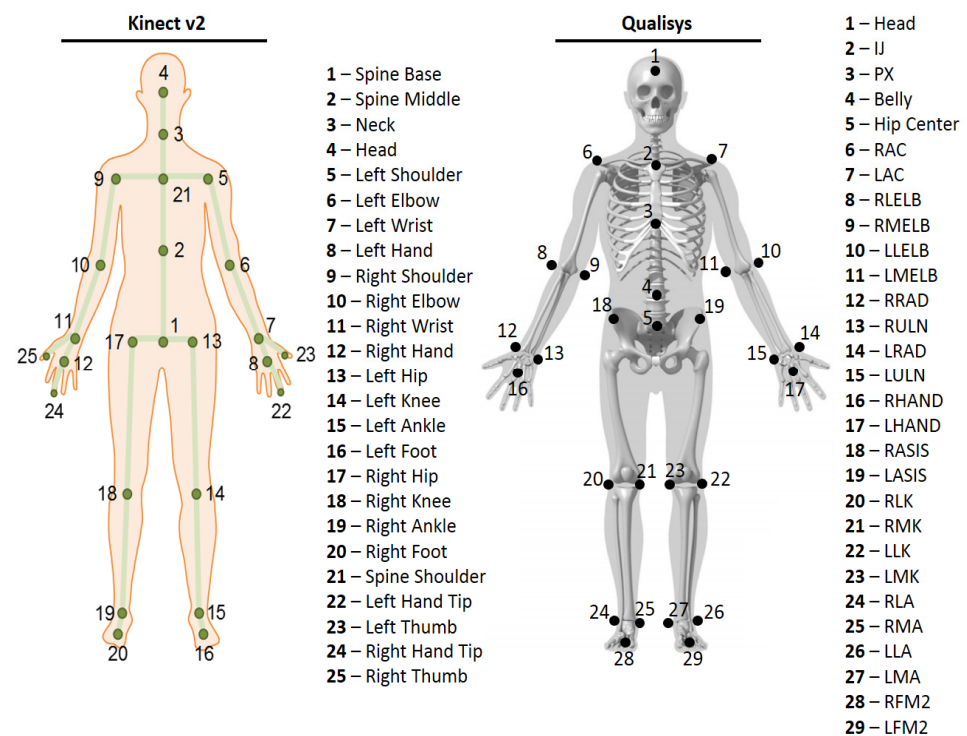


Figure 1. Body joints tracked by the Kinect v2, and retro-reflective markers placed at the subject's body used by the Qualisys system.

For synchronization purposes, an extra marker was dropped on the floor within the field of view of both systems used before the beginning of each gait task.

2.3. Data Acquisition and Processing

Two acquisition sessions took place at T0 and T1 for each patient, with an interval of one year and a half between them. For each session, patient, and gait trial, we acquired data provided by both of the used systems.

The 3D position of the reference system's markers was acquired at 200 Hz. The 3-D body joint, depth, and infrared data provided by the RGB-D camera were acquired at 30 Hz, using our KiT software application that enables the online visualization and acquisition of Kinect data [55]. Each body joint data frame includes the 3D position of the 25 joints tracked by the Kinect v2, which are shown in Figure 1. The data from the two systems were synchronized by considering the instant the extra marker touches the ground as the common reference. For more details on the synchronization process, please refer to [53].

The acquired data corresponding to walking towards the Kinect were automatically selected using the method described in [50]. Then, the performed gait cycles and associated phases were automatically identified. Only the gait cycles detected by both systems were considered in the analysis presented below. The average number of gait cycles per patient was 33 at T0 and 41 at T1. A gait cycle is defined by two consecutive heel strikes of the same foot. Each gait cycle includes two steps, which are defined by two consecutive heel strikes of opposite feet. For the RGB-D camera, the instants corresponding to heel strikes were estimated using the distance between ankles and a window of size ND1 frames, as described in more detail in [53]. The identification of the heel strike side (left or right) relied on the ankles' velocity, using a window of size ND2 frames. Both measures were previously processed using a moving average filter with a window size of NF1 and NF2, respectively (with the same value as in [53]). Toe offs were detected by finding the maximum absolute difference between the left and right shanks angle, using a window of size ND3, as described in [50].

The actual heel strike and toe off events were identified based on the foot vertical velocity computed over Qualisys data (ground truth), as described in [50,53].

For each gait cycle and system, we computed the 23 gait parameters described in [50]. The TBCM-ML and -V sway correspond to the standard deviation of the distance between the TBCM and RGB-D camera in the x - and y -axis (corresponding to the mediolateral and vertical directions), respectively. For each frame, the TBCM is the weighted average of the CM of 15 body segments as described in [56]. The CM of each body segment was computed according to [57]. The TBCM sway measures the variability of the TBCM motion and can therefore be useful for assessing posture, evaluating balance disorders, and/or predicting fall risk [57].

The measures used to compute the gait parameters were firstly processed using a Butterworth filter. To minimize parameter computation error, the filter's order and cutoff frequency were optimized for each parameter. This optimization consisted of selecting the pair of values for order and cut-off frequency that led to the lowest mean absolute between Kinect and Qualisys (for all subjects and gait cycles at T0), when considering the orders of 2, 4 and 6, as well as frequencies between 1 and 9 Hz (integer values). If filtering did not lead to a decrease in error higher than 1 cm for spatial, 1 cm/s for spatiotemporal, and 1 degree for kinematic parameters, then no filtering was applied to the corresponding measure. The Butterworth filter's results are presented in Tables A1 and A2 included in Appendix A.

2.4. Statistical Analysis

To investigate whether the considered RGB-D camera can be used as an alternative system for detecting relevant changes in the gait of a given ATTRv amyloidosis patient over time, we compared the results obtained at T0 and T1 for both Kinect v2 and Qualisys.

For each parameter, patient, and system, we obtained the difference between the mean values for T0 and T1 when considering all gait cycles. A negative/positive value indicates a decrease/increase in the parameter mean value between the two moments, which verifies whether the trend over time for the Kinect was the same as for Qualisys.

Furthermore, we investigated if the difference between T0 and T1 was statistically significant by carrying out the Mann–Whitney U non-parametric test over the parameter's median values for all gait cycles at T0 and T1. The test results obtained for both systems help to verify if the Kinect can detect actual significant changes in gait over time (results for the reference Qualisys system considered as the ground truth). The statistical test was performed using IBM SPSS Statistics for Windows, Version 25.0. (Armonk, NY, USA: IBM Corp) with a confidence interval of 95%.

Based on the interpretation of the Mann–Whitney U test results regarding the difference between T0 and T1—statistically non-significant, or significant increase/decrease—we performed the Cohen's Kappa inter-rater agreement test to determine the agreement between the RGB-D camera and reference systems. The results of this test were interpreted

according to Landis et al. as “poor” (<0.00), “slight” (0.00–0.20), “fair” (0.21–0.40), “moderate” (0.41–0.60), “substantial” (0.61–0.80) or “almost perfect” (0.81–1.00) [58].

3. Results

Regarding the gait parameter computation over the 3D joint data provided by the RGB-D camera, our approach requires only an average of 0.65 s to extract the considered parameters for a given gait cycle (including cycle detection). This result was obtained using a computer with an Intel® Core™ i7-4600U CPU 2.1–2.7 GHz and 8 GB RAM.

Table 3 shows the mean difference results obtained for each parameter, patient, and system. In this table, a statistically significant difference of the parameter’s value between T0 and T1 (p -value ≤ 0.001) is indicated with “↓” or “↑” next to the mean difference value (negative or positive difference, respectively).

Table 3. Difference between the mean value at T1 and T0, for each parameter, patient, and system (“Ref” stands for reference system and “RGB-D” for RGB-D camera-based system). If a statistically significant difference was found between the parameter’s values at T0 and T1 (Mann–Whitney U Test, p -value ≤ 0.001), the mean difference value is indicated with “↑” or “↓” (positive or negative difference, respectively). When there is no significant difference, or when there is a significant difference and the trend is the same (positive or negative), for both systems, the results are highlighted in grey. “—” indicates that it was not possible to perform the statistical test due to the small amount of available data.

Spatiotemporal Gait Parameter	Mean Difference (T1 – T0)											
	P1		P2		P3		P4		P5		P6	
	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D
Stride duration (s)	0.026	0.023	0.074↑	0.066↑	−0.060↓	−0.054↓	−0.083↓	−0.083↓	−0.067	−0.076	0.061↑	0.061↑
Step duration (s)	0.012	0.009	0.039↑	0.038	−0.026↓	−0.025	−0.043	−0.051↓	−0.030	−0.041	0.030	0.031↑
Stance duration (s)	0.025↑	0.019	0.053↑	0.054↑	−0.043↓	−0.064↓	−0.118↓	−0.045	−0.061↓	−0.043	0.027↑	0.027↑
Swing duration (s)	0.000	0.003	0.028↑	0.013	−0.021↓	0.005	0.048	−0.012	−0.005	−0.033	0.032	0.033↑
Single support duration (s)	0.000	0.0135	0.044↑	0.015	−0.050↓	0.004	0.079	−0.045	−0.016	−0.065↓	0.083↑	0.087↑
Double support duration (s)	0.026↑	0.009	0.019	0.030	−0.014	−0.064↓	−0.164	−0.021	−0.050↓	−0.010	−0.018↓	−0.014
Stride length (cm)	−11.7↓	−12.1↓	−16.5↓	−17.1↓	−1.37	−0.981	1.46	0.091	11.9↓	11.7↓	1.68	−3.64
Step length (cm)	−6.20↓	−6.72↓	−7.49↓	−8.97↓	−0.365	0.946	3.36	2.99	—	—	1.51	−3.98
Step width (cm)	−1.76↓	−0.695	−1.26	1.03↑	0.042	1.09	1.89	0.45	—	—	0.853	0.897
Gait speed (m/s)	−0.131↓	−0.134↓	−0.182↓	−0.185↓	0.013	0.009	0.027	0.035	0.128↑	0.136↑	−0.066	−0.069
Gait speed variability (m/s)	0.000	0.003	−0.022↓	−0.020↓	0.016↑	0.016↑	−0.003	0.000	0.007	0.005	0.021↑	0.015
Foot swing velocity (m/s)	−0.435↓	−0.385↓	−0.531↓	−0.334↓	0.014	0.119	0.029	−0.154	0.389↑	0.384↑	−0.114	−0.219
Arm swing velocity (m/s)	−0.237	−0.207	0.008	0.167	0.199↑	0.336↑	0.343	0.107	0.115	0.263	−0.223↓	−0.197↓
TBCM-ML * sway (cm)	0.248	−0.181	0.421	0.747	−0.039	−0.424	—	—	—	—	—	—
TBCM-V * sway (cm)	−0.028	−0.020	−0.376↓	−0.305↓	0.075	0.044	—	—	—	—	—	—
Spine shoulder angle	−14.1↓	−3.6↓	7.9↑	5.1↑	−13.8↓	−3.5↓	−8.8↓	0.7	−4.4	1.0	−12.6↓	−0.6
Spine middle angle	5.2↑	−2.4↓	7.7↑	3.2↑	14.2↑	−2.2↓	9.0↑	0.5	6.8	0.6↑	2.8↑	−0.3
Maximum elbow angle	7.7↑	0.8	7.9↑	4.8↑	6.5↑	2.4↑	14.3↑	3.7	7.9↑	15.8↑	7.3↑	1.1
Minimum elbow angle	10.8↑	1.6	1.7	3.2	−0.9	−4.7↓	10.4	0.6	15.5↑	7.8↑	12↑	4.5
Maximum knee angle	2.1	1.1	3.1↑	−1.3	−0.3	−1.4↓	1.3	0.2	2.6↑	−5.6↓	0.4	−3.4↓
Minimum knee angle	2.4	1.3	5.5↑	−1.4	−2.0↓	−1.6	3.6	2.1	2.4	−6.8↓	4.0↑	0.2
Hip angle range	2.0	−2.0	3.7	−7↓	0.5	−1.9↓	4.0	−3.2↓	1.3	1.5	0.7	0.9
Ankle angle range	0.4	−12.5↓	−6.7↓	−5.1	1.0	−13.6↓	−3.4	−4.1	0.9	−5.1	1.1	7.4

* TBCM-ML and TBCM-V stand for total body center of mass mediolateral and vertical sway, respectively.

For each parameter and patient, the mean difference values for the reference and RGB-D camera systems are highlighted in grey where a non-significant difference was detected for both, or when there was a significant difference and the trend (positive or negative) was the same for both.

Overall, the systems showed similar performance for 53 out of 82 cases in terms of spatiotemporal parameters, and 18 out of 48 cases for kinematic parameters. There was agreement for most patients in the case of the six spatiotemporal parameters; all patients for stride duration, gait speed, and arm swing velocity; five patients for stride length and foot swing velocity; and four patients for gait speed variability. For the remaining spatiotemporal parameters, there was agreement between the systems for half of the patients (stance duration, step length and width, and TBCM-V) or less (2 patients for step, single and double support duration, and TBCM-ML; 1 patient for swing duration). For the

29 cases where there was no agreement, the following was observed: the RGB-D sensor was unable to detect an actual significant difference fourteen times; it incorrectly detected a significant difference seven times; a significant difference was detected correctly but the trend over time was opposite eight times.

For kinematic parameters, the Kinect was in accordance with Qualisys for half of the patients for the spine shoulder and the maximum and minimum elbow angle, and only two or one patient for the remaining parameters. In most cases where there was no accordance (30 out of 48 cases), the Kinect did not detect an actual significant difference in the parameter's values (14 out of 30 cases), while the opposite happened for 10 cases. For the remaining six parameter/patient pairs, both systems found significant differences, but the trend over time was opposite (the mean parameter value decreased for Qualisys, while it increased for Kinect, or vice-versa).

Furthermore, when performing the Cohen's Kappa inter-rater agreement (CK-IRA) test over all gait parameters and subjects, a fair strength of agreement ($\kappa = 0.360$, 95% CI [0.194, 0.505], p -value ≤ 0.001) was achieved. When taking into account only the kinematic parameters, there was a moderate strength of agreement ($\kappa = 0.546$, 95% CI [0.440, 0.617], p -value ≤ 0.001). A substantial strength of agreement ($\kappa = 0.757$, 95% CI [0.645, 0.840], p -value ≤ 0.001) was obtained when considering only the spatiotemporal gait parameters. The strength of agreement was almost perfect ($\kappa = 0.932$, 95% CI [0.837, 0.970], p -value ≤ 0.001) when considering the following six parameters that showed the best accordance between systems when analyzing Table 3: stride duration, gait speed, arm swing velocity, stride length, foot swing velocity, and gait speed variability. Table 4 provides a representation of Table 3's results.

Table 4. Representation of the difference between the two used systems for each parameter and patient. When both systems have the same result it is shown in green, it is shown in yellow when they have the same tendency but one does not show a statistically significant difference, and in orange when the tendency and the difference are not the same. “—” indicates that it was not possible to perform the statistical test due to the small amount of available data.

Spatiotemporal Gait Parameter	Mean Difference (T1–T0)					
	P1	P2	P3	P4	P5	P6
Stride duration (s)	Green	Green	Green	Green	Green	Green
Step duration (s)	Green	Yellow	Yellow	Yellow	Green	Yellow
Stance duration (s)	Yellow	Green	Green	Yellow	Yellow	Green
Swing duration (s)	Yellow	Yellow	Orange	Orange	Green	Yellow
Single support duration (s)	Green	Yellow	Orange	Orange	Yellow	Green
Double support duration (s)	Yellow	Green	Yellow	Green	Yellow	Yellow
Stride length (cm)	Green	Green	Green	Green	Green	Orange
Step length (cm)	Green	Green	Orange	Green	—	Orange
Step width (cm)	Yellow	Orange	Green	Green	—	Green
Gait speed (m/s)	Green	Green	Green	Green	Green	Green
Gait speed variability (m/s)	Green	Green	Green	Orange	Green	Yellow
Foot swing velocity (m/s)	Green	Green	Green	Orange	Green	Green
Arm swing velocity (m/s)	Green	Green	Green	Green	Green	Green
TBCM-ML * sway (cm)	Orange	Green	Green	—	—	—
TBCM-V * sway (cm)	Green	Green	Green	—	—	—
Spine shoulder angle	Green	Green	Green	Orange	Orange	Yellow
Spine middle angle	Orange	Green	Orange	Yellow	Yellow	Orange
Maximum elbow angle	Yellow	Green	Green	Yellow	Green	Yellow
Minimum elbow angle	Green	Green	Yellow	Green	Green	Yellow
Maximum knee angle	Green	Orange	Green	Green	Orange	Orange
Minimum knee angle	Green	Orange	Yellow	Green	Orange	Yellow
Hip angle range	Orange	Yellow	Orange	Orange	Green	Green
Ankle angle range	Orange	Yellow	Orange	Green	Orange	Green

* TBCM-ML and TBCM-V stand for total body center of mass mediolateral and vertical sway, respectively.

4. Discussion

Regarding the conformity between the RGB-D camera-based system and the reference system, they were in agreement in most cases for spatiotemporal parameters (65%) and only in some cases for kinematic parameters (38%). These results were expected, since the validity of the Kinect for obtaining spatiotemporal parameters is better when compared with kinematic parameters, according to previous studies with healthy subjects [49] and ATTRV amyloidosis patients [50].

The lower agreement between systems concerning kinematic gait parameters may be explained by the fact that the computation of angle measures involves three joints (most measures used for spatiotemporal involve only one joint) and depends on the relative position of those joints in relation to each other. For these reasons, errors in joint position estimation are expected to have a greater negative impact on the computation of kinematic rather than spatiotemporal gait parameters.

Different factors can contribute to the Kinect not being as accurate as the reference system, including a low variable frame rate (≈ 30 Hz) and, in the particular case of our study, the use of a single camera. Using a single camera can lead to occlusions and variable estimation accuracy depending on the subject's distance to the camera (this distance varied during our acquisitions). Although multiple cameras could mitigate some of these problems, it would compromise our goal of achieving a low-cost and easy-to-set-up system that is suitable for use in clinical settings.

Another possible reason for lower accordance in the case of kinematic parameters is that the used Kinect configuration (frontal plane view) may not be the most adequate for obtaining accurate kinematic parameters. Pfister et al. showed that lower limb angle measures can be obtained with modest accuracy if the Kinect is positioned at a 45° angle to the longitudinal walking plane [30]. On the other hand, Mentiplay et al. carried out preliminary experiments with different Kinect angles but did not reach any conclusion regarding the best position to obtain particularly accurate kinematic data [36]. Therefore, further studies are needed to investigate whether there is an optimal configuration of the Kinect for obtaining kinematic gait parameters.

When considering spatiotemporal parameters, it is possible to see that there was full agreement (i.e., for all patients) between systems for the stride duration, gait speed, and arm swing velocity, and accordance for all patients except one in the case of stride length and foot swing velocity. For gait speed variability, the systems were in accordance for four out of the six patients. There was no accordance for half or more patients in the case of the step, swing, single support and double support duration, step length and width, and TBCM-ML and TBCM-V sway. Concerning the kinematic parameters, spine shoulder angle, and maximum and minimum elbow angles presented the best results (accordance between systems for half of the patients). All other kinematic parameters showed agreement for two patients, except the spine middle angle for which systems were in accordance only for patient P2.

It is interesting to note that the six most reliable gait parameters (stride duration, gait speed, arm swing velocity, stride length, foot swing velocity, and gait speed variability) show an almost perfect strength of agreement between systems. Therefore, these parameters can potentially be used to support the clinical gait assessment of ATTRv amyloidosis patients during the course of the disease.

By analyzing the follow-up results considering only the actual values (i.e., obtained with the reference system) at the two different assessment moments, we found that the parameters that evolved less overall (i.e., the difference was not significant for half or more patients) were step, swing, single and double support duration, stride length, step length and width, gait speed and its variability, foot and arm swing velocity, TBCM-ML, minimum elbow angle, minimum and maximum knee angles, as well as hip and ankle angle range. There was a significant increase from T0 to T1 in the case of the spine middle angle, as well as the maximum and minimum elbow and knee angles, for most patients. This increase may have occurred because of a search for balance, which translated into a widening of

the movements' amplitude. On the contrary, there was an overall significant decrease in the spine shoulder angle, suggesting that the patients tend to shorten their distance to the ground and lower their center of mass to increase balance, probably due to steppage. The tendency of wider steps and lower double support duration may have also contributed to that decrease.

Step length and width are important to consider if there are alterations to the walking base (i.e., the distance between the lower limbs) to increase walking stability [23]. In this sample, both step length and step width decreased for the patients who have a significant change in this parameter.

The biggest challenge in performing a detailed analysis of the gait of ATTRv amyloidosis patients is the complex context of this multisystemic condition. Therefore, we also performed a more clinically focused analysis of the intra-patient gait evolution, where we compared the obtained quantitative results with the qualitative scores obtained through clinical observation (presented in Table 2).

For the first patient (P1), the actual difference between T0 and T1 was not significant in the case of the ankle angle range. This result is in line with the clinical observation of P1's specific disease progression, which showed only small dorsiflexion worsening from 4 to 4—(see Table 2). In contrast with the reference system, the RGB-D camera-based system detected a significant change for the considered parameter. However, the same system was able to correctly detect non-significant or significant differences for most spatiotemporal parameters (12 out of 15) and five kinematic parameters (spine shoulder and spine middle angles, maximum and minimum knee angles, and hip angle range).

For the second patient (P2), the worsening profile is discrete, as was the case with P1. This patient already had a profound distal motor deficit that worsened with the loss of plantar flexion. Moreover, at T1, a proximal deficit was noticed through the loss of muscular force and consequent loss of knee flexion ability. However, in contrast with the qualitative analysis, the quantitative results show an actual significant increase in the maximum and minimum knee angles, which suggests that quantified motion information provides information that may be difficult to obtain through observation only. Nevertheless, the RGB-D camera was not in agreement with the reference system for the knee angle parameters.

Although no changes regarding dorsiflexion were observed clinically in P2, plantar flexion worsened (1 to 0). The latter was translated into a significant decrease in the actual ankle angle range. Despite the difference measured for the RGB-D system not being statistically significant, the mean difference value was similar to that obtained with the reference system (−5 and −7 degrees, respectively). The worsening of plantar flexion may have contributed to a significant increase in stride, step, stance, swing and single support duration, and a significant decrease in stride and step length, gait speed, gait speed variability, and foot swing velocity. These significant differences were correctly detected by the RGB-D system for all these parameters, except swing and single support duration, and step width.

The third patient (P3) showed only weakness at the toes from one assessment moment to the other. This patient was in stage I of the PND and ATTRv amyloidosis scores and therefore showed fewer restraints overall during gait when observed by the neurologist. Nevertheless, the quantitative analysis for this patient performed with the reference system showed a significant difference from T0 to T1 for half of the gait parameters (seven out of fifteen spatiotemporal, and four out of eight kinematic), which again shows that a quantitative analysis may help detect changes in gait that are not visible to the naked eye. The significant changes were correctly detected by the RGB D camera for six out of eleven parameters, which also correctly detected no significant changes for 7 out of 12 parameters.

It is important to notice that patient P3 began taking tafamidis ten months before the first assessment. Although the clinical observation is in line with the finding that there is a higher efficacy of the drug at the earliest stage of ATTRv amyloidosis [12], the quantitative analysis showed significant changes for several gait parameters. Therefore,

the obtained results suggest that the introduction of an objective tool for gait analysis of ATTRV amyloidosis patients may also benefit drug efficacy evaluation.

Regarding the fourth patient (P4), most spatiotemporal parameters showed no significant difference (11 out of 13 analyzed parameters). However, actual significant changes were observed for only a few parameters (two out of thirteen spatiotemporal, and three out of eight kinematic), which is in line with this patient's clinical observation (no alteration of MRC scores between T0 and T1). Nonetheless, P4 suffered a major worsening in the appointment that followed the data collection at T1. Therefore, the significant changes detected with the reference system may have been an anticipation of that evolution, although this is speculative.

The clinical assessment of the fifth patient (P5) showed a slight worsening of dorsiflexion (four to three score on the MRC scale, from T0 to T1), which led to a discrete yet observable worsening of gait (steppage was very low at T0 and clear at T1—see Table 2). Despite the observed worsening of dorsiflexion, the actual difference between T1 and T0 for the ankle angle range is not significant. However, other gait parameters had significant changes (stance and double support duration decreased, while stride length, gait speed, foot swing velocity, maximum and minimum elbow angle, and maximum knee angle increased), which may be related to the prominence of the steppage profile at T1. The RGB-D camera correctly detected significant changes for six out of eight parameters and non-significant changes for eight out of eleven parameters.

For the sixth patient (P6), gait did not change in clinical observation. However, the distal segmental force in dorsiflexion and plantar flexion showed worsening between T0 and T1, which may explain the differences found for some quantitative gait parameters (six out of thirteen spatiotemporal, and five out of eight kinematic). Although the analyzed parameters do not have a direct relation with those used for clinical observation, the alterations measured quantitatively are consistent with the observed progression. Regarding the RGB-D system, it correctly detected significant or non-significant changes for 11 parameters in the case of P6.

Note that TBCM-ML was either not analyzed for some patients (P4, P5, P6) or the difference between T0 and T1 was not significant (P1, P2, P3). In contrast, TBCM-V was found to be significantly different for one patient (P1). This suggests that the vertical alterations in ATTRV amyloidosis gait are higher than mediolateral ones, which seems to follow the visual indication of the importance of the absence of dorsiflexion and the consequent rise of the knee for a safe foot-landing, in steppage. Furthermore, the computation of the TBCM sway parameters showed us the need to collect a greater number of gait cycles from the patients in the future, to assist with a more complete analysis.

Although the changes found in the TBCM parameters cannot be directly linked to an already described specific feature of disease progression (i.e., walking with crunches or the need for a wheelchair in the main dislocations; see score definitions in [59]), they show that there are differences within the same disease stage. Therefore, there is potential interest in exploring new tasks and/or parameters that may add more objective information to the assessment of disease progression.

This study has some limitations, including the small number of patients and data collection sessions over time. Nevertheless, the obtained results show that there is potential in using an RGB-D camera-based system as an alternative to a reference system for detecting significant changes over time for several spatiotemporal parameters. Another limitation is that we do not have a clear clinical threshold for ATTRV amyloidosis patients' gait performance, since evaluation is usually performed only by observation of the gait pattern. Still, the quantitative information provided by this type of system can be useful not only to support clinical assessment, but also to define a more fine-specific staging of the disease. Furthermore, although the Kinect v2 has been discontinued, it is important to note that there is a new version of the Kinect (Azure Kinect DK) on the market, which uses a depth-sensing approach similar to that of Kinect v2 (i.e., time-of-flight) [60].

The inter- and intra-patient parameter variations found were expected, since each patient has a specific disease progression time and a different reaction to the evolution of gait impairments. Although all patients analyzed have the same mutation, their phenotypes vary, translating into different disease onset and progression scenarios. Longitudinal studies provide insights into inter-individual changes and help to identify parameters that can assess the disease stage as well as the response to medication.

Concerning the time between data collection moments, a smaller interval would assist in the detection of more subtle gait changes. Nevertheless, the most adequate interval between gait follow-up assessments is still an open issue for this disease, and the results obtained in this study show that the RGB-D camera system was able to detect relevant changes for some gait parameters even when no changes were visible to the naked eye.

5. Conclusions

In this study, we explored the use of an affordable, portable, simple to operate, and non-intrusive system based on a single RGB-D camera to complement the clinical evaluation of ATTRv amyloidosis progression. More specifically, we investigated if our RGB-D camera-based gait analysis system is a viable alternative to a multi-camera marker-based reference system for detecting relevant changes in the gait of ATTRv amyloidosis patients during their follow-up.

Gait data were collected from six ATTRv amyloidosis patients at two different time points using our gait analysis system based on a single RGB-D camera (Kinect v2) and a multi-camera marker-based Qualisys system (reference). Several gait parameters were extracted from the 3D data provided by the two systems. For each parameter, patient, and system, we verified if there was an increase or decrease in the mean parameter value between the two assessment moments and if the difference was statistically significant or not.

We found that the RGB-D system is in accordance with the reference system for half or more patients for all spatiotemporal parameters, except for step, swing, single and double support duration, and TBCM ML sway. On the other hand, there was agreement between both systems for less than half of the patients for all kinematic parameters, except for spine shoulder angle and maximum and minimum elbow angles (accordance for half the patients). An almost perfect strength of agreement was obtained for the best six gait parameters when considering the existence or not of a statistically significant difference between the two analysis moments and all patients.

To the best of our knowledge, these results are the first to show the potential of using a gait analysis system based on a single RGB-D camera for detecting statistically significant progression in the gait of ATTRv amyloidosis patients over time, demonstrating that this type of system can become a useful tool for detecting the evolution of ATTRv amyloidosis patients regarding several spatiotemporal gait parameters, during follow-up, and in a clinical environment. They can also be useful as a basis to propose a new and more fine-grained scale based on gait characteristics in the future.

This system can also contribute to enhanced knowledge regarding disease progression (individually and collectively). Moreover, it can be useful for the evaluation of the outcome of new treatments or treatment adjustments, as well as the development of targeted interventions and new strategies to improve the patients' gait and consequently their quality of life.

Although the obtained results suggest that a single RGB-D camera can provide valuable information for gait assessment during ATTRv amyloidosis patient follow-up, further studies with a larger number of patients and data acquisition sessions per patient, as well as greater clinical insight, are necessary. The improvement of gait stability detected in the increased muscle strength and range of joint motion, resulting from exercise programs, has been suggested for diabetic patients with gait impairments [61,62] and ATTRv amyloidosis patients' quality of life may benefit from the same approach. Furthermore, it has previously been shown that RGB-D cameras can be used to assess balance in healthy subjects [35].

Therefore, it would also be interesting to investigate if an RGB-D camera can be used to support the assessment of ATTRv amyloidosis patients during balance tests, which may additionally help to deepen the understanding of the evolution of stability during gait in ATTRv amyloidosis. Additionally, in future work, it would also be important to explore ways of further improving the gait parameters, especially kinematic parameters, obtained from the RGB-D camera data, by investigating alternative methods for noise removal, such as other filters, or machine learning.

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Appendix A

Table A1. Mean absolute error between Kinect and Qualisys for the spatiotemporal gait parameters, without filtering and when varying the Butterworth filter's order between 2 and 6 (even integer values), and cut-off frequency between 1 and 9 Hz (integer values). The result corresponding to the chosen value for each gait parameter is underlined. TBCM-ML and TBCM-V stand for total body center of mass medio-lateral and vertical sway.

		Stride Length (cm)	Step Length (cm)	Step Width (cm)	Gait Speed (m/s)	Gait Speed Variability (m/s)	Foot Swing Velocity (m/s)	Arm Swing Velocity (m/s)	TBCM-ML Sway (cm)	TBCM-V Sway (cm)
No Filter		1.48	2.93	1.00	0.013	0.080	0.935	0.279	0.45	0.24
Butterworth filter (order, cut-off frequency)	2, 1	1.48	3.54	11.0	0.019	0.036	0.709	0.213	0.39	0.64
	2, 2	1.48	3.04	5.66	0.014	0.015	0.367	0.111	0.41	0.41
	2, 3	1.48	2.88	3.41	0.013	0.011	0.234	0.090	0.42	0.33
	2, 4	1.48	2.84	2.26	0.013	0.012	0.224	0.091	0.43	0.29
	2, 5	1.48	2.83	1.60	0.013	0.016	0.283	0.104	0.44	0.29
	2, 6	1.48	2.83	1.24	0.013	0.023	0.368	0.124	0.44	0.26
	2, 7	1.48	2.81	1.06	0.013	0.035	0.476	0.151	0.44	0.25
	2, 8	1.48	2.82	0.99	0.013	0.050	0.611	0.187	0.44	0.24
	2, 9	1.48	2.91	0.99	0.013	0.067	0.783	0.236	0.45	0.24
	4, 1	1.48	5.11	12.9	0.016	0.045	0.790	0.211	0.41	0.74
	4, 2	1.48	3.37	5.68	0.013	0.014	0.408	0.093	0.43	0.37
	4, 3	1.48	3.04	2.88	0.013	0.011	0.231	0.080	0.44	0.28
	4, 4	1.48	2.82	1.79	0.013	0.012	0.194	0.084	0.44	0.26
	4, 5	1.48	2.90	1.30	0.013	0.013	0.223	0.094	0.44	0.25
	4, 6	1.48	2.78	1.09	0.013	0.014	0.280	0.107	0.44	0.25
	4, 7	1.48	2.72	1.00	0.013	0.019	0.354	0.125	0.44	0.25
	4, 8	1.48	2.78	0.98	0.013	0.031	0.439	0.148	0.44	0.24

Table A1. Cont.

	Stride Length (cm)	Step Length (cm)	Step Width (cm)	Gait Speed (m/s)	Gait Speed Variability (m/s)	Foot Swing Velocity (m/s)	Arm Swing Velocity (m/s)	TBCM-ML Sway (cm)	TBCM-V Sway (cm)
4, 9	1.48	2.88	0.97	0.013	0.046	0.542	0.174	0.44	0.24
6, 1	1.48	6.93	13.9	0.016	0.051	0.789	0.209	0.41	0.79
6, 2	1.48	3.61	5.88	0.013	0.013	0.430	0.090	0.43	0.36
6, 3	1.48	3.18	2.76	0.013	0.012	0.228	0.077	0.44	0.27
6, 4	1.48	2.85	1.70	0.013	0.012	0.189	0.082	0.44	0.25
6, 5	1.48	2.78	1.26	0.013	0.013	0.212	0.091	0.44	0.25
6, 6	1.48	2.86	1.07	0.013	0.013	0.257	0.103	0.44	0.25
6, 7	1.48	2.75	0.99	0.013	0.016	0.319	0.117	0.44	0.25
6, 8	1.48	2.74	0.98	0.013	0.023	0.397	0.139	0.44	0.24
6, 9	1.48	2.76	0.97	0.013	0.039	0.485	0.163	0.44	0.24

Table A2. Mean absolute error between Kinect and Qualisys for the kinematic gait parameters, without filtering and when varying the Butterworth filter's order between 2 and 6 (even integer values), and cut off frequency between 1 and 9 Hz (integer values). The result corresponding to the chosen value for each gait parameter is underlined.

	Spine Shoulder Angle (Deg)	Spine Middle Angle (Deg)	Maximum Elbow Angle (Deg)	Minimum Elbow Angle (Deg)	Maximum Knee Angle (Deg)	Minimum Knee Angle (Deg)	Hip Angle Range (Deg)	Ankle Angle Range (Deg)
No Filter	4.4	19.1	6.7	6.1	5.7	9.0	6.2	40.8
Butterworth filter (order, cut-off frequency)	2, 1	4.4	19.1	6.4	7.7	6.2	21.9	6.6
	2, 2	4.4	19.1	6.3	6.8	5.8	14.5	3.6
	2, 3	4.4	19.1	6.3	6.6	5.7	11.9	3.9
	2, 4	4.4	19.1	6.3	6.5	5.7	10.9	4.5
	2, 5	4.4	19.1	6.3	6.4	5.7	10.3	5.0
	2, 6	4.4	19.1	6.3	6.3	5.7	10.0	5.4
	2, 7	4.4	19.1	6.4	6.3	5.7	9.7	5.7
	2, 8	4.4	19.1	6.4	6.3	5.7	9.5	5.9
	2, 9	4.4	19.1	6.5	6.2	5.7	9.2	6.1
	4, 1	4.4	19.1	6.5	7.8	6.3	24.7	9.1
	4, 2	4.4	19.1	6.4	6.7	5.6	13.6	3.9
	4, 3	4.4	19.1	6.3	6.5	5.7	10.4	4.0
	4, 4	4.4	19.1	6.3	6.4	5.7	9.9	4.9
	4, 5	4.4	19.1	6.3	6.4	5.7	9.9	5.3
	4, 6	4.4	19.1	6.3	6.4	5.7	9.8	5.5
	4, 7	4.4	19.1	6.3	6.4	5.7	9.7	5.7
	4, 8	4.4	19.1	6.4	6.3	5.7	9.6	5.8
	4, 9	4.4	19.1	6.4	6.3	5.7	9.5	5.9
	6, 1	4.4	19.1	6.6	7.9	6.4	26.2	10.1
	6, 2	4.4	19.1	6.5	6.7	5.4	13.6	4.0
	6, 3	4.4	19.1	6.3	6.5	5.6	9.7	4.1
	6, 4	4.4	19.1	6.3	6.4	5.7	9.5	5.0
	6, 5	4.4	19.1	6.3	6.4	5.7	9.8	5.4
	6, 6	4.4	19.1	6.3	6.4	5.7	9.9	5.5
	6, 7	4.4	19.1	6.3	6.4	5.7	9.7	5.7
	6, 8	4.4	19.1	6.3	6.4	5.7	9.6	5.8
	6, 9	4.4	19.1	6.4	6.3	5.7	9.5	5.9

Appendix B

Table A3. *p*-value obtained on the Mann–Whitney U test for the difference between the mean value at T1 and T0, for each parameter, patient, and system (“Ref” stands for reference system and “RGB-D” for RGB-D camera-based system).

	P1		P2		P3		P4		P5		P6	
	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D
Stride duration (s)	0.009	0.019	0.000	0.000	0.000	0.001	0.000	0.000	0.002	0.001	0.000	0.000
Step duration (s)	0.053	0.160	0.000	0.002	0.000	0.108	0.001	0.000	0.024	0.002	0.010	0.000
Stance duration (s)	0.001	0.032	0.000	0.000	0.000	0.000	0.000	0.068	0.000	0.008	0.001	0.000
Swing duration (s)	0.954	0.127	0.001	0.407	0.000	0.215	0.007	0.307	0.442	0.005	0.010	0.000
Single sup. duration (s)	0.651	0.061	0.001	0.368	0.000	0.269	0.194	0.073	0.352	0.000	0.000	0.000
Double sup. duration (s)	0.000	0.531	0.077	0.061	0.111	0.000	0.003	0.560	0.000	0.341	0.000	0.246
Stride length (cm)	0.000	0.000	0.000	0.000	0.087	0.395	0.786	0.620	0.000	0.000	0.681	0.151
Step length (cm)	0.000	0.000	0.000	0.000	0.771	0.609	0.241	0.078	—	0.000	1.000	0.022
Step width (cm)	0.000	0.235	0.105	0.048	0.834	0.008	0.091	0.659	—	0.000	0.080	0.141
Gait speed (m/s)	0.000	0.000	0.000	0.000	0.272	0.442	0.021	0.003	0.000	0.000	0.002	0.002
Gait speed var. (m/s)	0.924	0.267	0.000	0.000	0.000	0.000	0.442	0.611	0.013	0.094	0.001	0.007
Foot swing vel. (m/s)	0.000	0.000	0.000	0.001	0.688	0.075	0.988	0.129	0.000	0.000	0.158	0.002
Arm swing vel. (m/s)	0.024	0.024	0.507	0.180	0.000	0.000	0.013	0.304	0.104	0.004	0.000	0.000

Table A3. Cont.

	P1		P2		P3		P4		P5		P6	
	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D	Ref	RGB-D
Total body center of mass medio-lateral sway (cm)	0.090	0.358	0.258	0.027	0.753	0.050	—	0.359	—	0.147	—	0.203
Total body center of mass vertical sway (cm)	0.404	0.444	0.000	0.000	0.001	0.020	—	0.172	—	0.025	—	0.002

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