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Egyptian consensus on treat-to-target approach of gout: evidence-based clinical practice guidelines for the management of gout

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Abstract

Introduction: New therapies, management approaches, and evidence regarding the management of gout have become available over the past years. This triggered the need for an updated recommendation for gout management. Through an up-to-date consensus evidence-based clinical practice guideline for the management of gout including recommendations for management of gout flares, optimum usage of urate lowering therapy for chronic gout, as well as patient education and lifestyle guidance. A wide systematic literature review was performed, and evidence-based recommendations were extrapolated, based on 16-key questions identified according to population, intervention, comparator, and outcomes (PICO) approach. These were evaluated by a panel consisted of 17 rheumatology experts via online surveys over a 2-round Delphi process. The purpose of this study is to offer an updated, consensus-evidence-based, and in the meantime patient-focused, expert recommendations for the treat-to-target approach of gout management.

Results: Results revealed that after round 2 ended, a total of 30-recommendation items, categorized into 10 domains, were obtained. Agreement with the recommendations (rank 7–9) ranged from 90 to 100%. Consensus was reached (i.e., ≥ 75% of respondents strongly agreed or agreed) on the wording, the grade of recommendation, and level of evidence of all the 30 clinical standards identified by the scientific committee.

Conclusions: This guideline provides updated evidence-based recommendations for the prevention and treatment of acute as well as chronic gout. This guideline provides an approach for physicians and patients making decisions on the management of gout. It will also facilitate improvement and uniformity of care.

Keywords: Gout, Gouty arthritis, Urate, Therapy, Treatment guidelines, Treat-to-target, Outcomes, Egyptian guidelines for gout

Background

Gout is the commonest form of inflammatory arthritis affecting adults worldwide [1]. Gout's main clinical presentation is in the form of recurrent acute inflammatory arthritis triggered by hyperuricemia and subsequent accumulation of monosodium urate crystal deposition in the joint fluid, cartilage, bones, bursae, tendons, and other sites [2]. In > 90% of patients with gout, hyperuricemia is attributed to reduced fractional clearance of urate [3]. Gout flare is an exceptionally painful and incapacitating form of inflammatory arthritis, which usually affects one joint but occasionally it may mimic the polyarthritis

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pattern of rheumatoid arthritis. If not adequately managed, it is a disorder that usually progresses rather than regresses. In its acute form, the goal of gouty treatment is swift and safe cessation of pain and disability. Without medical management, the gout flare usually resolves completely within a few days to several weeks, especially in early disease. Upon resolution of the gouty flare, the patient enters in a symptom-free phase (interval, intercritical, or between flares). However, in the majority of patients' flares recur, with episodes, flares may be more severe and prolonged, with subsequent shortening of the asymptomatic periods [4] and consequent joint damage.

Impairment of health-related quality of life is usually associated with chronic gout and tophi leading to chronic disability [5–8], absence from work, and reduced productivity as well as increased use of healthcare resources [9]. In addition to some co-morbidities such as obesity, chronic renal impairment, hyperlipidemia, diabetes mellitus, high blood pressure, cardiovascular disease, osteoarthritis, hypothyroidism, psoriasis, anemia, chronic pulmonary diseases, and depression are frequently associated with gout [10]. Gout has also been reported to be associated with an increase in all-cause mortality and urogenital malignancy [10, 11].

Despite its high prevalence and impact, gout is understudied and often undertreated [12–14]. Furthermore, over the past 20 years, the incidence of gout has more than doubled. This high incidence, together with the frequently associated comorbidities and cardiovascular risk factors, represents a significant public health challenge [15]. However, in spite of the fact that the etiology of gout is well-known and there are non-expensive effective medical therapies to treat gout, there are still gaps in the provided care [16–18]. Though, the application of a treat-to-target (T2T) strategy has attracted the attention to its implementation in several rheumatic diseases, the value of defining therapeutic targets for gout has much less information available. Despite recently published treatment recommendations [19–22], many challenges, such as recurrence prevention of attacks and design a management protocol tailored to the individual patient's condition and its associated comorbidities, remain, when considering the current treatment strategy of patients with gout. Therefore, there is a need optimize and identify clear treatment targets to close this gap in the management of patients living with gouty arthritis.

The overarching objective of this work is to develop an up-to-date consensus evidence-based clinical practice guideline for the management of gout. This would be of value not only for health care providers managing acute inflammatory arthritis in general, but also for regulatory bodies, health-related organizations, and interested patients' groups. This project was carried out under the CEG (Consensus, Evidence-based, Guidelines) initiative set up in Egypt which aims at promoting evidence-based practice in rheumatology by developing treat-to-target clinical practice guidelines addressing relevant clinical problems.

Methods

Design

The consensus, evidence-based treatment guidelines for gout was developed adopting a multistep process strategy. The study design was formulated based on the CEG guideline development process protocol which involves a scientific evidence and consensus, based on the existing scientific evidence and clinical experience. The manuscript conformed to the preferred reporting items for systematic reviews and meta-analyses guidelines for reporting systematic reviews [23].

Development stages

Core team

It was formed of 4 experts with recognized experience in gout management. The core team coordinated and supervised the teamwork; helped in developing the scope of the project and initial patient/population, intervention, comparison, and outcomes (pico) clinical questions; and reached the final agreed key questions to include in the guidelines. For each PICO question, the core team preidentified outcomes as critical for the systematic literature review. The team also chose the expert panel and drafting the manuscript.

Key questions used in the guideline

This guideline was centered on a series of structured key questions that include the target population, the intervention, diagnostic test, or exposure under investigation; the comparison(s) used; and the outcomes used to measure efficacy, effectiveness, or risk. Answering these clinical questions was following these steps: formulation of clinical questions, structuring of questions, search for evidence, critical evaluation and selection of evidence, presentation of results, and recommendations. These questions, shown in Table 1, formed the basis of the systematic literature search and consequently the clinical care standards. Evidence-based recommendations for the diagnosis and investigation of gout have not been included in this guideline.

Literature review team

Led by an experienced literature review consultant and based on the specific research questions identified to focus on the management of gout, the literature review was conducted with the assistance of an expert in methodology. To acquire proper evidence-based background

Table 1 Key questions used to develop the guidelines

Domains	Key questions
Targeted patients:	Who are the targeted patients?
Treatment target:	What is the treatment target?
Treatment of gout flare:	What is the best strategy for treatment of gout flare?
	What is the recommended duration of treatment of gout flare?
Treatment of recurrent gout	What is the approach for treatment of recurrent gout?
	What is the advised timing of starting ULT therapy?
	When to consider switching ULT treatment?
	What is the management approach in case of failure to achieve targeted serum urate despite ULT dose escalation?
Prophylaxis against gout flare	What is the best approach for prophylaxis against gout flare?
Management of refractory gout	What is the best management approach for refractory gout?
Long-term management of gout	What is the strategy for long-term management of gout?
Patient's education and lifestyle advice:	What are the main points to be included in the patients' education program for gout patients?
Comorbidities screening	Should people with gout be screened for comorbidities?
Management of gout in patients with CKD and patients on dialysis	What is the best approach for management of gout in patients with CKD?
	Is there specific management strategy for people with gout on dialysis?
Recommendations for specific medications and pregnancy:	Are there specific recommendations for specific medications used commonly for patients with gout?

knowledge for considerations, a systematic literature search was carried out from database launch to 28th May 2021, using PubMed/ MEDLINE, EMBASE, and Cochrane databases. Following the data abstraction, reviewing the published recommendations, and the quality of evidence rating [24, 25], revision was carried out by the experts responsible for the literature review, who provided a comprehensive list of propositions for the management of gout based on available research evidence and their own clinical expertise. The level of evidence was determined for each section using the Oxford Centre for Evidence-based Medicine (CEBM) system [25].

Data sources and search strategies

The search strategy was planned to capture all studies in which the study population were adults living with Gout. The PICO questions (Table 1) were used to conduct the literature search. Literature search strategies were carried out to locate randomized clinical trials evaluating the efficacy of gout management as well as quality improvement outcomes/approaches. The following medical terms were used: 1. General: gout, gouty arthritis, tophi, tophus, tophaceous, urate, sodium OR monosodium OR potassium OR ammonium AND urate, urate crystal, hyperuricemia; Q 1: diagnosis, sensitivity and specificity; Q 2: Treat to Target, T2T, outcome; Q 3 and 4: gout flare, glucocorticoids, adrenal Cortical Hormone, Anti-Inflammatory therapy, NSAIDs, Non-Steroidal, Cyclooxygenase 2 Inhibitors, arcoxia, NSAID, cyclooxygenase 2 inhibitors, cox-2 inhibitors, aspirin, diclofenac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, Naproxen, Piroxicam, etodolac, interleukin-1, colchicine, efficacy, serum urate (sUA), pain, Joint swelling, tenderness. Time: acute treatment: 24–72 h follow-up, chronic treatment: any follow-up time, delayed vs. immediate treatment; Q 5–12: chronic gout management, tophus/tophi/tophaceous, recurrence, urate lowering therapy, ULT, monitoring, discontinuation, Xanthine oxidase inhibitors allopurinol, uricosuric, febuxostat, probenecid, colchicine, pegloticase, efficacy, safety, urate level, combination medication, probenecid/colchicine, XOIs/anti-inflammatories, Sulfinpyrazone, co-interventions, switch, switching ULT, prophylaxis, refractory, long-term, thiazides; silent hyperuricemia, serum urate, urate crystals, hyperuricemia; Q 13: Monitoring, Urate, acute-Phase Proteins, ESR, CRP, serum Albumin, pain score/measurement, diagnostic Imaging/ Radiography/ Ultrasound/ ultrasonography/ US, Magnetic Resonance Imaging, Tomography, X-Ray CT, contrast media/ Radionuclide Imaging, patient Compliance/ adherence to therapy, treatment refusal; Q 14: patient education, alcohol drinking, alcohol related disorders, exercise, physical education, physical fitness, diet, sports, smoking, smoking cessation, weight loss, anti-obesity agents, diet therapy, nutrition therapy, fasting, dairy products, milk, fructose, coffee, dietary supplements, fortified food, antioxidants, amino acids, vitamins, fatty acids, unsaturated, pain, patient global assessment; Q 15: comorbidities, diabetes mellitus, insulin resistance, liver disease, kidney disease, hypertension, cardiovascular diseases, myocardial ischemia, heart

failure, gastrointestinal diseases, dyspepsia, peptic ulcer, peptic ulcer hemorrhage, duodenogastric, drug interactions, hematologic diseases, precursor cell lymphoblastic leukemia-lymphoma, leukemia; Q 16 and 17: CKD, renal failure, renal impairment, dialysis.

Keywords used according to PICO and were used in different ways. Literature searches on 14th May 2021 for PubMed and Cochrane Library databases, and on 28th May 2021 for Embase. Duplicate screening of literature was done. Additional relevant studies were retrieved by reviewing the reference lists of studies identified with the database search strategies that met the inclusion criteria.

Study selection

Relevant studies were selected by applying inclusion and exclusion criteria to the literature retrieved with the search strategies.

Inclusion criteria

Articles included were systematic reviews, randomized controlled trials (RCTs), uncontrolled trials, observational studies including cohort, case control and cross-sectional studies, or those where economic evaluation was made.

Exclusion criteria

Editorials, commentaries, conference abstracts, and non-evidence-based narrative/personal reviews, manuscripts lacking English version, were excluded. Studies of hyperuricemia were included only if they were related to the management of gout.

Expert panel

The core leadership team nominated 19 participants. The criteria for their selection included the following: have professional knowledge and experience (at least 8 years of experience) in the field of rheumatology, management of inflammatory arthritis, and in particular gout as well as active participation in scientific research on rheumatic diseases. The expert panel assisted with developing the scope of the project and refining the PICO questions. PICO questions were drafted into recommendation statements and were sent to the expert panel with the evidence report who voted on the recommendations.

Target audience

The guideline has been developed to assist healthcare professionals who treat and manage patients with gout. The guideline should provide a helpful resource for patients and caregivers for patients with gout in the National Health Service.

Developing the clinical care standards framework

Based on the answers to the structured key questions and the literature review, a structured template was developed to facilitate standardized identification of guideline components. For each guideline component, the format in which the recommendations/information will be provided and extracted have been identified.

Delphi process

The Delphi technique is the best method widely used for gathering information on a targeted topic. It relies on the key assumption that projections from a group are generally more accurate than those from individuals. Therefore, the aim of the Delphi method is to make consensus forecasts from a group of experts in an interactive and structured way. It is based on a series of questionnaires or "rounds" addressed to experts. The Delphi method generally involves the following stages: (1) A panel of experts is assembled. (2) Forecasting tasks/challenges are set and distributed to the experts. (3) Experts return initial forecasts and justifications. These are analyzed and summarized to provide feedback. (4) Feedback is provided to the experts, who reviewed their forecasts considering the feedback. (5) Final forecasts are constructed by aggregating the experts' forecasts. The key features of this method are the anonymity of participants and the controlled feedback [26–28].

Consensus process

Two Delphi rounds were carried out to establish consensus regarding the T2T (treat-to-target) strategy in gout. The structured Delphi approach ensures that the opinions of participants are equally considered. Through online questionnaires, the Delphi process was conducted. The first round of the electronic questionnaire included 16 items involved in the T2T strategy of gout.

Voting process

Live online-delivered voting was carried out in 3 rounds that were strictly time limited. All members of the task force were invited to participate and were pre-informed of the time of opening and closure of each round of votes. Access links were sent out for each round, and anonymous votes were gathered and processed. Comments on re-phrasing, potential ambiguity, and unidentified overlaps were gathered regarding each statement at the same time in the voting process. Only the members of this study had the right to vote on the statements.

Rating

Each statement was rated from 1 to 9 with 1 indicative of "complete disagreement" and 9 indicating "complete

agreement." Generally, 1–3 represented disagreement, 4–6 represented uncertainty, and 7–9 represented agreement. Voting on all statements was not mandatory, and the members were encouraged to refrain if they feel that a statement falls outside their area of expertise. An "uncertainty" vote represents "inconvenience about the accuracy of the recommendation." All statements were reviewed by the scientific committee after each round of voting. In all the votes' rounds, particularly wherever they vote a disagreement, the members were urged to leave comments. This enabled the panel to identify an instance of misinterpretation of statement and invalidate the vote on that statement.

Definition of consensus

Definition of consensus was established before data analyses. It was determined that consensus, consequently, to become a recommendation in this guideline, would be achieved if at least 75% of participants reached agreement (score 7–9) or disagreement (score 1–3) [25–29]. A statement was retired if it had a mean vote below 3 or a "low" level of agreement. Statements whose rate came in the uncertainty score, (4–6), were revised in view of the comments. While the statements of recommendations which were rated (7–9), after the second round, were defined as "high" if after the second round of votes [28–30].

Chronogram of Delphi rounds

The first round took place between 24th and 29th September 2021 (4 days). The items which did not reach consensus in this first round were revised in view of the comments and included in the second round. The second round took place on 6th of October 2021 (1 week after the first round) and lasted for 4 days (6th–10th October 2021).

Ethical aspects

This study was performed in accordance with the Helsinki Declaration. The Clinical, Evidence-based, Guidelines (CEG) initiative protocol was approved the local ethical committee: ethical approval code: 34842/8/21, ethical board Tanta University. Written ethics approval from the experts sharing in this work was deemed unnecessary according to national regulations. A verbal informed consent was required from all the participants included in the study according to the Egyptian Ethical Committee regulations. All the participants were kept anonymous, in compliance with data protection regulations.

Results

Literature research and evidence selection

In the study selection process, we found 3118 potentially relevant studies by search strategy. Then, 2870 were excluded: 324 duplicates and 2546 by screening of title and abstracts (studies did not examine population or intervention of interest, did not match study design of interest, or did not report outcome measures of interest). Therefore, 248 relevant studies were included for full article review. Further, 226 studies were excluded as citations did not provide evidence matching a PICO; consequently, 22 studies were included in this work (Fig. 1).

Expert panel characteristics

The Delphi form was sent to expert panel ($n = 19$), of whom 17 (89.5%) completed in the two rounds. The respondents were drawn from different governorates and health centers across Egypt: Ain Shams university ($n = 6$, 35.3%), Cairo University ($n = 2$, 11.8%), Tanta University ($n = 2$, 11.8%), Benha University ($n = 1$, 5.9%), Mansoura University ($n = 1$, 5.9%), Fayoum University ($n = 1$, 5.9%), Suez Canal University ($n = 1$, 5.9%), Zagazig University ($n = 1$, 6.25%), Minia University ($n = 1$, 6.25%), in addition to ($n = 1$, 6.25%) international expert from the UK. All the experts' panel (100%) were rheumatologists.

Delphi round 1

The key clinical question comprised of 16 questions stratified under 11 domains (Table 1) including targeted patients, treatment target, treatment of gout flare, treatment of recurrent gout, prophylaxis against gout flare, management of refractory gout, long-term management of gout, patient's education and lifestyle advice, comorbidities screening, management of gout in patients with CKD and patients on dialysis, as well as recommendations for specific medications and pregnancy. Each domain entails one or more elements. In this round, the participants were asked to rate the overall principles considered in the decision-making for T2T management of gout. The response rate for round 1 was 89.5% from the experts' panel (17/19). Consensus was reached on the domains (as $\geq 90\%$ of respondents strongly agreed or agreed), only one question about patient's education was requested to be amended and re-order its position, otherwise all the suggested questions were accepted by the panel and no questions were retired.

Delphi round 2

Considering the input from round 1, *a list of 30 proposed recommendations were developed based on the review of the literature, 1 for targeted patients and 1 for the treatment target, while 5 for the management of gout*

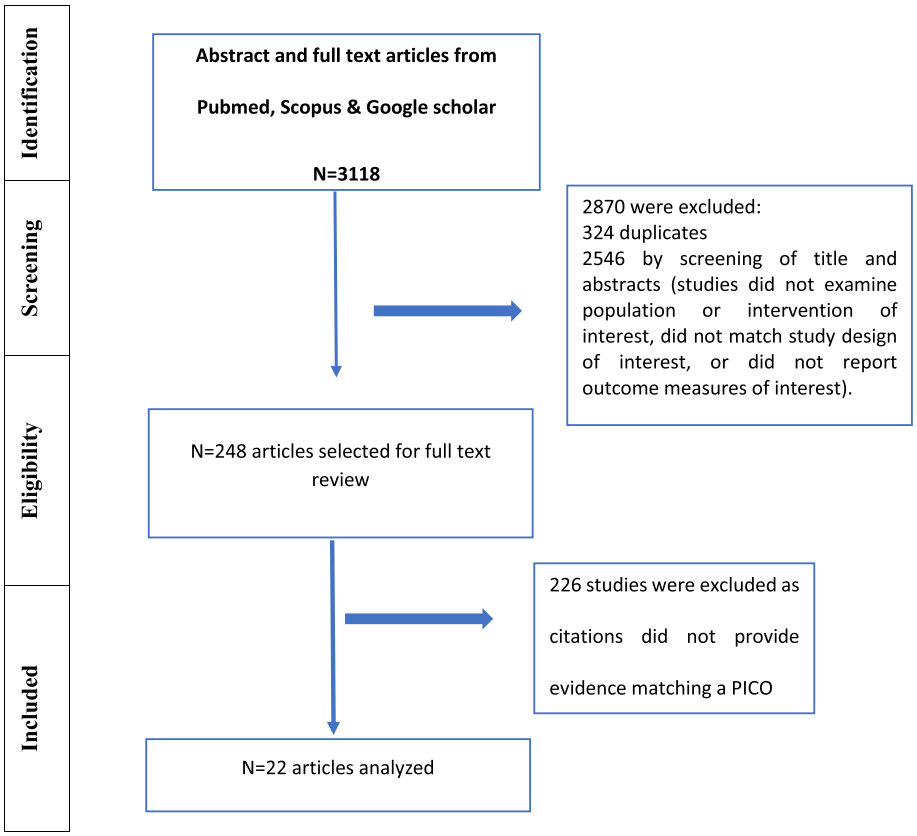

Fig. 1 Flow chart for the study selection process

flare, 2 relating to education, diet and lifestyle modification, 11 for the management of recurrent, inter-critical and chronic gout, 8 for management of gout in CKD and dialysis patients, and 2 for specific medications and pregnancy recommendations. The response rate for round 2 was 100% from the experts' panel (17/17). Consensus was reached (as ≥ 90% of respondents strongly agreed or agreed) on the wording of all 30 recommendations. No statement retired from the suggested ones. Table 2 also shows the level of evidence assigned to each statement, in accordance to the Oxford Centre for Evidence-Based Medicine (CEBM) criteria as well as mean + standard ± deviation and level of agreement.

Application of the primary recommendations to clinical practice guidelines

Clinicians require clear and readily accessible information that is applicable for standard practice. Therefore, treat to target guidelines for the management of gout should clearly identify who are the patients appropriate for evaluation, the required investigations, available options for therapy, as well as other interventions that should be offered for that individual patients regarding lifestyle changes and management of other associated comorbidities. Figure 2 shows an algorithm of the recommendations for the management pathway of acute and recurrent gout including T2T treatment approach.

Discussion

This work was carried out aiming at developing an updated treat-to-target guideline for gout patients. This guideline was developed in view of the new medications that have become available as well as expansion of the evidence-base for the efficacy and safety of the available therapies. Also, epidemiological studies revealed increasing incidence, prevalence, and severity of gout, not only worldwide, but also in Egypt [10, 31] despite the availability of safe, effective, inexpensive, and potentially curative therapy. Furthermore, worldwide, there is a treatment gap in the care of patients living with gout. Research studies have consistently revealed that less than 50% of people with gout receive the expected urate-lowering therapy (ULT) [33–39] and that many of them do not achieve the targeted levels of serum urate (sUA) levels. In addition, there is accumulating evidence of potential barriers to effective care. Emerging data revealed that these

Table 2 Consensus for 30 revised draft recommendations was reached after two rounds of a Delphi exercise

Domains	Recommendations	LE	GOR	Mean ± SD	% of agreement	Level of agreement
1- Targeted patients:	**Who are the targeted patients?** Patients with any of the following: gout flare, recurrent gout flares (> 1 flare), subcutaneous tophi; refractory gout, gout in patients with CKD.	1	A	8.9 ± 0.3	100	H
2- Treatment target:	**What is the treatment target?** All people with gout should be managed adopting a treat-to-target strategy with dose titration and subsequent dosing adjustment guided by serial serum urate assessments to achieve both: a. Clinical cure; as well as b. The targeted serum urate level is achieved with a fixed, standard dose of ULT (urate-lowering therapy). Clinical cure: gout flares stop, tophi resolved. Target serum urate <6mg/dL (360 µmol/L); preferable < 5mg/dL (300umol/L) for patients with severe gout (tophi, chronic arthropathy, frequent gout flare). Serum urate should remain > 3 mg/dL (180 µmol/L) on the long term, as a potent antioxidant [31]. All patients taking ULT should continue taking their therapy lifelong to maintain the serum urate at the targeted level. A comprehensive management protocol adopting treat to target approach should include patient education, shared decision-making, and a treat-to-target strategy.	1	A	8.7 ± 0.5	100	H
3- Treatment of gout flare:	**What is the best strategy for the treatment of gout flare?** Patient education: The gout flare should be treated as early as possible. The patient should be aware of the importance of continuing any established ULT during the gout flare. The patients should be informed and educated on how to self-medicate at the first warning symptoms. Affected joints should be rested, elevated, and exposed in a cool environment, e.g., ice-packs. Treatment Choice: Should be considered bearing in mind: 1. The presence of contraindications and comorbidities, 2. The patient's previous experience with treatments, 3. Time of initiation after the onset of the gout flare and the number and type of joint(s) involved. 4. Colchicine and NSAIDs should be avoided in patients with severe renal impairment. 5. Colchicine should not be prescribed for patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporin or clarithromycin. Medication choice: 1. Colchicine (within 12 h of flare onset) at a loading dose of 1 mg followed 1 h later by 0.5 mg on day 1 and/or 2. A NSAID (tNSAID or Cox-2 inhibitor) (plus proton pump inhibitors (PPIs) if appropriate) 3. Oral corticosteroid (30–35 mg/day of equivalent prednisolone for 3–5 days) or 4. Intra-articular aspiration and injection of corticosteroids. Follow up in 4 weeks (2–5 weeks??): Assess for response to therapy. Assess for comorbidities (CVS factors: hypertension, lipids), diabetes Mellitus, obesity. Assess for lifestyle factors: exercise, diet, alcohol, sugar intake. Review current medications: stop thiazide diuretic. Blood check for serum urate, renal functions. No ULT is advised if this was the first gout flare. Advice regarding prophylaxis: Initiation of ULT is advised close to the time of the first diagnosis in patients presenting at [32]: - A young age (< 40 years), or - A very high SUA level (> 8.0 mg/dL; 480 µmol/L) and/or comorbidities (renal impairment (CKD > 3, hypertension, ischaemic heart disease, heart failure). - Tophi - Renal stones	4 4 4 1 1 1	C C C B A A	8.7 ± 0.5	100	H

Table 2 (continued)

Domains	Recommendations	LE	GOR	Mean ± SD	% of agreement	Level of agreement
	What is the recommended duration of treatment of gout flare? 7–14 days (until flare resolves; otherwise, a rebound flare can occur)	1	A	8.8 ± 0.4	100	H
4- Treatment of recurrent gout	**What is the approach for the treatment of recurrent gout?** Urate-lowering therapy (ULT): Initiating ULT is recommended for patients with any of the following: recurrent gout flares (> 1 flare) subcutaneous tophi; evidence of radiographic damage (any modality) attributable to gout. ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation adopting a shared decision-making approach. ULT is not recommended for patients with asymptomatic hyperuricemia (no prior gout flares or subcutaneous tophi). ULT is not recommended for patients experiencing their first gout flare. Allopurinol is the preferred first-line agent, over all other ULTs, including patients with moderate-to-severe CKD (stage ≥ 3). All ULTs should be started at a low dose and then titrated upwards until the targeted serum urate level is reached. The targeted serum urate should be maintained lifelong.	1	A	8.7 ± 0.6	100	H
	What is the advised timing of starting ULT therapy? Starting ULT treatment is best delayed until inflammation has settled as ULT is better discussed when the patient is not in pain. Initiation of ULT therapy: First line ULT: Allopurinol. Start at a low dose of 50–100 mg/day. Titrate the dose of Allopurinol in 50-100mg every 4-weeks. Target serum urate < 6 mg/dL (360 µmol/L); preferable < 5mg/dL (300 µmol/L) for patients with severe gout (tophi, chronic arthropathy, frequent gout flares). Split the allopurinol dose if more than 30 mg dose/day. Maximum dose 900 mg /day (in patients with normal renal functions). Consider flare prophylaxis while initiating allopurinol therapy. Do not stop Allopurinol therapy during gout flare.	4	C	8.4 ± 0.8	100	H
	When to consider switching ULT treatment? - Intolerability to Allopurinol or - CKD preventing adequate dose escalation - Persistently high serum urate concentrations (> 6 mg/dL) despite maximum-tolerated dose as per the guidelines. - Patients who continue having frequent gout flares (> 2 flares/year) OR - Patients who have non- resolving subcutaneous tophi. Switching ULT therapy: - Consider switching to febuxostat 40–80 mg once daily. - Increase febuxostat dose to 120 mg once daily after 4-weeks if the targeted serum urate level has been achieved. - For people with gout with a history of CVD or a new CV event, caution should be considered, decision adjusted tailored to the patient's cardiac status, when febuxostat is advised. - Intolerability to febuxostat: Consider switching to uricosuric therapy (sulfinpyrazone or probenecid or benzbromarone) - Titrate dose every 4-weeks according to serum urate	1	A	8.6±0.6	100	H
	What is the management approach in case of failure to achieve targeted serum urate despite ULT dose escalation? - Consider Uricosurics either as monotherapy or in combination with allopurinol - Add-on therapy to partially responsive ULT therapy can result in improved serum urate control, - Benzbromarone (50–200 mg/day) is a more potent uricosuric as compared with probenecid (1–2 g/day), bearing in mind its hepatotoxicity, so avoid its use in patients with hepatic disease, initiating treatment with low dose regimens, monitoring liver enzymes during treatment, and avoiding the association of benzbromarone with other hepatotoxic medicines [33]. - For patients considered for uricosuric therapy, there is no need to check for urinary urate. - For patients considered for uricosuric therapy, it is not advised to recommend alkalinisation of the urine (lack of evidence for efficacy). - Patients with known renal calculi or moderate-to-severe CKD (stage > 3) should not be treated with uricosurics. - Adequate hydration is highly recommended for patients on uricosuric therapy, at least 1.5 L of fluid daily.	1	A	8.8 ± 0.4	90	H

Table 2 (continued)

Domains	Recommendations	LE	GOR	Mean ± SD	% of agreement	Level of agreement
5- Prophylaxis against gout flare	**What is the best approach for prophylaxis against gout flare?** - Prophylaxis against flares should be fully explained and discussed with the patient - Prophylaxis is recommended during the first 3-6 months of ULT [32]. - Medication choices for prophylactic treatment are:- colchicine, 0.5–1 mg/day, (the colchicine dose should be reduced in patients with renal impairment); or - Prophylaxis with NSAIDs at low dosage (particularly If colchicine is not tolerated or is contraindicated), plus PPIs. - One-off intramuscular injection of methylprednisolone 120 mg, then small doses of oral prednisolone. - In cases receiving statin therapy, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine. - Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors should be avoided. - Prophylaxis with NSAIDs at low dosage, if not contraindicated, should be considered.	2	A	8.6 ± 0.7	100	H
6- Management of refractory gout	**What is the best management approach for refractory gout?** Refractory gout flare: In patients with frequent flares and contraindications to colchicine, NSAIDs, and corticosteroids (oral and injectable), IL-1 blockers should be considered for treating flares. Current infection is a contraindication to the use of IL-1 blockers. Refractory Chronic gout: Switching to pegloticase is recommended for people with gout for whom ULT treatment, uricosurics, (including combinations) and other interventions have failed to achieve the targeted serum urate, and who continue to have frequent gout flares (≥ 2 flares/year) or who have non-resolving subcutaneous tophi.	1	A	8.8 ± 0.4	100	H
7- Long-term management of gout	**What is the strategy for long-term management of gout?** When to consider? Treatment targets achieved: clinical cure (gout flares stop, tophi resolved); targeted serum urate (< 300 µmol/L). Action: consider lowering the ULT dose to maintain the targeted serum urate (between 300 and 360 µmol/L). Check serum urate every 6–12 months to ensure it is maintained within the targeted range (if elevated, adjust the ULT dose accordingly) [34]. Continue ULT lifelong.	2	A	8.6 ± 0.7	100	H
8- Patient's education and lifestyle advice:	**What are the main points to be included in the patients' education program for gout patients?** Information should be given to every person living with gout about the disease pathophysiology, the availability of effective treatments, and the associated comorbidities, and the basis of treating the gout flares and lowering the level of urate crystals through a lifelong treat to target management approach. Lifestyle advice: Optimize body weight (adopt a weight loss program) is advised for gout patients who are overweight/ obese, regardless of disease activity. Significantly limiting alcohol intake (regardless of disease activity). Limiting purine intake: avoid heavy meals and excessive intake of meat and seafood (regardless of disease activity). Limiting sugar-sweetened drinks. Adding vitamin C supplementation is not advised.	4	C	8.8 ± 0.4	100	H

Table 2 (continued)

Domains	Recommendations	LE	GOR	Mean ± SD	% of agreement	Level of agreement
9- Comorbidities screening	**Should people with gout be screened for comorbidities?** Every person with gout should be systematically screened for associated comorbidities: - - Cardiovascular risk factors, coronary heart disease, heart failure - Hypertension - Hyperlipidemia - Diabetes Mellitus - Renal impairment - Stroke - Peripheral arterial disease - Obesity - Smoking	2	B	8.9 ± 0.4	100	H
10- Management of gout in patients with CKD and patients on dialysis	**What is the best approach for the management of gout in patients with CKD?** Patients with CKD: - The allopurinol maximum dosage should be adjusted to creatinine clearance. If the SUA target cannot be achieved at this dose, the patient should be switched to febuxostat or given benzbromarone with or without allopurinol. - Lowering the allopurinol starting dose according to the renal function level reduces the risk of allopurinol hypersensitivity, and the subsequent gradual increase in the dose above the dose based on eGFR is advised as it helps to reduce serum urate levels in most people with gout without any increase in toxicity. Gout therapy in CKD (grade 3–5): ULT therapy:- Allopurinol is the first option, however, the starting dose and the maintenance doses should be distinguished. - Starting regime of allopurinol should be adjusted to the individual patient's eGFR. This will help to reduce the likelihood of developing a gout flare or allopurinol hypersensitivity syndrome (AHS), advised approach is as below:	2	A	8.6 ± 0.5	100	H

eGFR	Allopurinol starting dose
<5	50 mg/week
5_15	50mg twice weekly
16_30	50mg every 2 days
31_45	50 mg/day
46_60	50mg and 100mg on alternate days
61_90	100 mg/day
91_130	100 mg/day
>130	100 mg/day

Table 2 (continued)

Domains	Recommendations	LE	GOR	Mean ± SD	% of agreement	Level of agreement
	- gradually increasing the allopurinol dose is advised till the target is achieved. - Gout sufferers with creatinine clearances less than 30 mL/min typically require lower doses of allopurinol to achieve the same reductions in serum urate levels. - should monitor for pruritis, rash, elevated hepatic transaminases, and eosinophilia. There are insufficient data for febuxostat in patients with creatinine clearance <30 Uricosuric therapy: - Benzbromarone: contraindicated if CrCl <20 mL/min - Lesinurad: contraindicated if CrCl <45 mL/min - Probenecid: Not effective if CrCl < 30 mL/min **Prophylaxis:-** - Colchicine: CrCl < 30 mL/min: initial dose: 0.3 mg/day, caution if up-titrated; monitor closely for adverse effects. - NSAID: avoid **Management of flares**:- - Steroids: Dosage adjustment for CKD not required - ACTH: Dosage adjustment for CKD not required					
	Is there a specific management strategy for people with gout on dialysis? - Allopurinol: Intermittent (hemodialysis) HD: should be administered post-dialysis, start with 100 mg alternate days post-dialysis; daily HD: additional 50% of dose may be required post-dialysis; daily peritoneal dialysis (PD): start with 50 mg/day; all types of renal replacement therapy (RRT): up-titrate dose with 50 mg–increments every 2–5 weeks, measure serum urate pre-dialysis. - Febuxostat: some successful reports of dialysis patients using febuxostat up to 80mg/day. No fully published trials. - Uricosuric therapy: contraindicated in dialysis patients. - Sevelamer: may be the phosphate binder of choice for patients with advanced CKD and gout, based on its urate-lowering effect. **Prophylaxis:-** - Colchicine: Not removed by dialysis; increased risk of myo/neurotoxicity. - NSAID: may be considered. **Management of flares**: - Steroids: Dosage adjustment for CKD not required - ACTH: Dosage adjustment for CKD not required	2	B	8.6 ± 0.5	100	H
11- Recommendations for specific medications and pregnancy:	**Are there specific recommendations for specific medications used commonly for patients with gout?** - When a gouty patient receiving loop or thiazide diuretics, substitute the diuretic is advised. - An interaction between allopurinol and furosemide that results in increased serum urate and plasma oxypurinol concentrations has been reported. - For hypertension consider losartan or calcium channel blockers - For hyperlipidemia, consider a statin or fenofibrate. **Recommendations for Gout during pregnancy:** gout is very uncommon in pre-menopausal women and in pregnancy, apart from patients with familial juvenile hyperuricaemic nephropathy, consequently, data are scarce. - Conservative measures including ice are safe for managing gout flares. - NSAIDs can be used in the mid-trimester. - Steroids are generally safe to use in pregnancy - The recommendations for lifestyle modifications including dietary changes are also safe.	2	B	8.8 ± 0.4	100	H

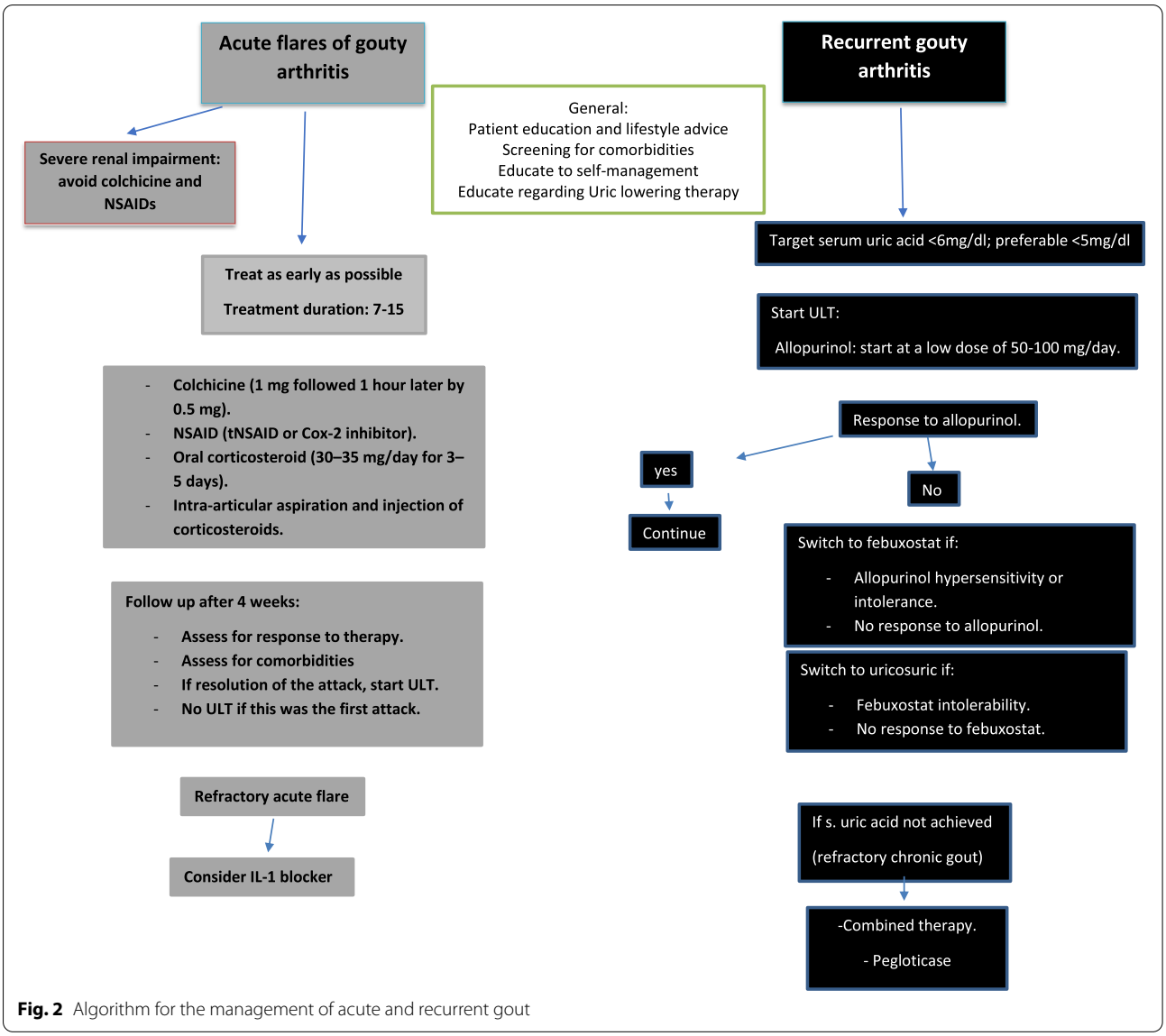

Fig. 2 Algorithm for the management of acute and recurrent gout

barriers can be tackled, with high chances of improved outcomes and better provision of quality of care based on clinical practice guidelines.

Gout is known to be the earliest disease to be recognized as a clinical entity. First identified by the Egyptians in 2640 BC [40], podagra (gout flare occurring in the first metatarsophalangeal joint) was later recognized by Hippocrates in the fifth century BC, who referred to it as "the unwalkable disease" [41]. The prevalence of gout in Egypt was reported to be 1–4% of the general population [42]. This agrees with the worldwide prevalence of gout which was recorded in the range of 1–4% and incidence range 0.1–0.3%. Men has higher incidence of gout than women by 3:1 to 10:1. Prevalence of gout increased by each decade of life, by 11–13% and incidence increasing to 0.4% in people older than 80 years [43]. This comes in concordance with the local experience. Outcomes of an earlier study carried out on Egyptian patients revealed that the incidence rates of gout were 136.7/100,000 after monitoring 271 elderly patients during 2009–2010 for gout flare [15].

Gout should be considered as a "sentinel" disease which rarely occurs in isolation but points to a likely aggregation of various cardiovascular risk factors as well as other comorbidities. Thus, in most patients, management of the initial gout flare will only represent a minor component of treatment. In a cross-sectional study [31] carried out in Egypt to assess the prevalence of hyperuricemia among hospitalized elderly patients as well as to assess its association with Metabolic syndrome. Data

from 200 hospitalized elderly patients were analyzed, and the results revealed that the prevalence of hyperuricemia was 21.0% in elderly men and 15.1% in elderly women. An independent association between hyperuricemia and metabolic syndrome was revealed by multivariate logistic regression analysis. Therefore, a comprehensive, multispecialty approach is required to reduce the morbidity and mortality of gout and its associated health hazards in these patients [15]. This not only highlights the high prevalence of people with gout, but also widens the scale of the targeted patients who should be screened and managed.

Evidence has accumulated that the provision of information to patients with gout is suboptimal [44]. Published qualitative studies have defined a range of patient and provider barriers to effective care [45–47]. Emerging preliminary data demonstrate that these barriers can be overcome, and outcomes improved, with better provision of information and a package of care based on guideline recommendations [48]. The developed guideline included several target points regarding patient education and provision of information about gout and its treatment. The recommendations stated in this work emphasized that patient education should not be limited to risk factors and lifestyle changes, but also expands to include information regarding management of gout flares, and the urgency to treat the gout flares as soon as they occur, as well as the optimal use of urate-lowering therapies. Results of this consensus highly recommended that the ULT option should be discussed and offered to all patients with gout as part of their education about the condition and that patients are fully involved in the decision as to when to start the ULT. In concordance, this has been also strongly highlighted in recently published guidelines [32, 49–51] reflecting the importance of patients' education and self-management.

T2T has booked its place as a guiding strategy for the treatment of inflammatory arthritic conditions and incorporates several distinct principles: identifying a target and a tool to measure it; evaluating the target at a pre-specified time point; a commitment to alter the therapy if the target has not been achieved; and shared decision-making. Gout is one of the best examples of treat to target approach in rheumatology, with an identified gold standard for management and monitoring. In agreement with recent recommendations [32, 50, 51], this guideline adopted a treat to target strategy and formulated a therapy-based management algorithm. A clear definition of resistant/irresponsive and severe cases has also been identified. Monitoring and follow up parameters, both clinical and lab, were also identified and included in this work. Many professional organizations have supported T2T approach and defined it as a fundamental therapeutic strategy [32, 50, 51]. Recent RCTs data comparing treat-to-target protocols versus the standard care [52, 53] recommends using a treat-to-target strategy with ULT to achieve and maintain a sUA target of 300–360 mmol/l (< 6 mg/dL) to control patient outcomes. Lower sUA levels were reported to accelerate the resolution of tophi [53, 54] and are associated with less frequent gout flares [51, 54], suggesting that lower SU thresholds (e.g., < 300 mmol/l) may be preferable for patients with more burdensome gout. Less stringent sUA target of 360 mmol/l can be implemented particularly after some years of successful ULT when tophi have resolved, and the patient remains symptom free [50].

The consensus endorsed the option of starting allopurinol after complete disappearance of the gout flare symptoms or when the inflammation is not too bad. This was based on the preference to avoid triggering further gout flares during the therapy initiation, the high prevalence of comorbidities that require further control, as well as the quality of the research studies suggesting this approach. This is in agreement with the EULAR recommendations [51, 55] and in contrast to the most recent ACR guidelines for the management of gout [32]. Two small clinical studies [56, 57] have reported that it is rational to start allopurinol during the gout flare. However, the core team noted that the low patients' number in these studies ($n = 51$ and $n = 31$, respectively) which could not confirm that the obtained data was for allopurinol 200–300 mg, which could not be generalized to the more potent urate-lowering drugs, such as febuxostat or a combination of xanthine oxidase inhibitor and an uricosuric [51]. Furthermore, this guideline emphasized the go-low strategy of starting ULT and titrating up to attain the targeted serum urate. This strategy lessens the risk of sustaining any of the treatment-related adverse effects, e.g., flare-up risk or hypersensitivity reaction [57, 58]. Titration of ULT should take place over weeks to months, not any longer. Checking serum urate levels is advised after each step of dose titration [58]. Prophylactic therapy (e.g., use concurrent anti-inflammatory medication) to minimize the risk of developing ULT-related flares, for 3–6 months, is advised. Longer periods may be advised in in the setting of frequent ongoing flares.

Gout is linked to a number of important comorbidities including diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, kidney disease, and obesity. Therefore, patients presenting with gout are very likely to develop another treatable, though serious, condition. The guideline stresses that all people with gout should be screened for comorbidities at least annually, and consequently, treated appropriately. Identifying these comorbidities early is not only important to for appropriate management of the comorbidity, but also as they

have an impact on the therapeutic options for gout. The metabolic link for such close link between gout and its associated comorbidities was highlighted in previous studies [31, 59], where hypertension was proposed as the commonest comorbidity. The guideline includes also recommendations for treatment of gout in patients with renal impairment as well as dialysis. Regarding allopurinol therapy in patients living with renal impairment, particularly patients with CKD stage ≤ 4, low starting dose (50 mg) has been recommended and then careful gradual increase until the targeted sUA of 300 mmol/l is reached. For patients in who allopurinol is not tolerated or whose renal impairment prevents allopurinol dose escalation sufficient to achieve the therapeutic target, Febuxostat can be used as an alternative second-line xanthine oxidase inhibitor. Interleukin (IL) 1 inhibition may be of benefit in selected patients. We use anakinra, an IL-1 receptor antagonist protein, only in gout patients with frequent and/or documented gout flares in whom other available treatments have failed, are contraindicated, or in whom "rebound flares" occur even when glucocorticoid treatment is appropriately tapered. Canakinumab has been approved in the European Union for use in patients with more than three gout flares annually that are refractory to treatment with alternative agents [60]. For patients with severe symptomatic tophaceous gout in who standard ULTs are not enough to control hyperuricemia, whether alone or in combination, treatment with pegloticase can be considered by physicians with experience and facilities for dealing with infusion reactions. This agrees with recent recommendations for treatment of gout in patients living with renal impairment [61].

Conclusion

Gout is one of the few rheumatic diseases that can be described as a curable disease. This work was developed aiming at offering updated, concise, patient-focused, evidence-based, expert recommendations for the management of gout. As data in this guideline provided best and most updated practices in management, therefore implementation of this guideline in clinical practice will optimally lead to improved quality of care for people with gout. The broad representation of the consensus panel would have a role in disseminating of the results of this work to such a large number of local rheumatologists, with consequent high chances of increased uptake and implementation of the guidelines.

Abbreviations

PICO: Population, intervention, comparator, and outcomes; CEBM: Center for Evidence-based Medicine; T2T: Treat-to-target; CEG: Consensus, Evidence-based, Guidelines; sUA: Serum urate; ULT: Urate lowering therapy; US: Ultrasound/ultrasonography; NSAIDs: Non-steroidal anti-inflammatory drugs; CKD: Chronic kidney disease.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr. YElM, Dr. NAG, Dr. MM, Dr. MEG, Dr. MM, Dr. ME, Dr. MH, Dr. WH, Dr. SAT, Dr. NF, Dr. RA, Dr. BM, Dr. YA, Dr. RG, Dr. NE, Dr. SS, and Dr. SG. The first draft of the manuscript was written by Dr. SG and Dr. YEM. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Helsinki Declaration. The Clinical, Evidence-based, Guidelines (CEG) initiative protocol was approved the local ethical committee: ethical approval code: 34842/8/21, ethical board Tanta University.

Consent for publication

Not applicable.

Competing interests

The authors declare that the corresponding author Dr. Salwa Galal, and the co-authors Dr. Mohammed Hassan and Dr. Rehab Ali, are Associate Editors in Egyptian Rheumatology and Rehabilitation. Dr. Mona Mansour is the Editor-in-Chief of the journal, while Dr. Mohammed Mortada and Dr. Yasser El Miedany are among the Editorial Board of the journal.

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