Numerous observations suggest that chronic kidney disease (CKD) is an epidemic condition [1]. Although its prevalence varies according to geographical region, it has been reported that about 8–10% of the population show some degree of renal function impairment [1]. It is worth noting that CKD not only portends poor prognosis but it has also been demonstrated that CKD patients are among the most complex subjects (complexity being defined as number of comorbidities, presence of mental illness, number of types of physicians involved in each patient’s care, number of prescribed medications, number of emergency department visits, rate of death, rate of hospitalization, and rate of placement in a long-term care facility) to be managed, and consumes a large proportion of health care resources [2].

Contrary to diabetes or other metabolic diseases as prevalent as CKD, renal function impairment is often asymptomatic or pauci-symptomatic until very late stages of the disease. However, in the course of the disease many metabolic abnormalities may develop and aggravate patients’ well-being and prognosis [3]. Needless to say, great effort is being devoted to characterizing clinical symptoms, developing diagnostics, as well as treatments, to prevent CKD occurrence or progression toward end stage renal disease (ESRD).

The aim of this special issue is to collect data and share ideas on different aspects of these topics. The 25 papers published (Table 1) and the 26 (highest citations of 9) citations document will be of interest to investigators and readers interested in the complexity of CKD. Four articles [4–7] investigated the usefulness of various biomarkers to assess renal function or complications associated with CKD in adult, as well as pediatric, patients. Indeed, current strategies to assess renal function rely on serum creatinine levels a marker highly influenced by factors such as age, gender, race, comorbid conditions and/or use of concomitant medications. These articles highlight the need for a more accurate approach to assess the presence and severity of renal impairment [8]. Similarly, nephrologists’ lack of an accurate prognostic score system that integrates serological and histopathological pieces of information is documented in two other studies [9,10] published within this special issue.

Four other articles [11–14] report on the complicated interplay between CKD and other comorbid conditions. Although prevalence varies according to the region of the world, diabetes and Human Immunodeficiency Virus (HIV) infection are among the most common factors associated with renal dysfunction [12–14]. All comorbid conditions need to be taken into account to individualize and improve patient care. However, these articles call for more and dedicated studies to address how to appropriately manage highly comorbid CKD patients, especially in consideration of the fact that these subjects are often excluded by randomized clinical trials (RCT).
Other articles investigate the prevalence and impact of common metabolic abnormalities that frequently complicate the course of CKD in children or adults [15–17]. CKD should be perceived as a multifaced metabolic disease that accelerates aging. Anemia, hypoglycemia and phosphate metabolism abnormalities are only some examples of factors that have been associated with Cardio-Vascular (CV) senescence and/or morbidity and mortality [15–17]. Indeed, as renal function declines, several toxins may accumulate and exert detrimental effects on various metabolic pathways including promoting inflammation and renal damage progression [18–20]. In these perspectives, balanced nutrition may modulate the intestinal microbiota [21,22], reduce some toxin production, and accumulation, and hold promise to impact renal and overall survival of CKD patients [21,22].

Several other therapies have been proposed to tackle the abysmal risk of renal, cardiovascular and all-cause events at which CKD patients are exposed. Overall, eight out of 25 articles (32%) address the impact of different treatment strategies on various outcomes [23–29]. However, none of these reports on results of an RCT. Although this may be expected for a special issue of a journal of internal medicine, it also reflects the paucity of RCTs in the nephrology arena and the desperate call for more and ad hoc studies to investigate the impact and potential interaction of available drugs on renal function and outcomes of CKD patients.

In conclusion, the articles published in this issue reflect the complexity of CKD and the limitations of available tools to detect renal dysfunction and metabolic abnormalities associated with CKD, as well as the paucity of data to properly treat these patients. Nevertheless, they expand current understanding in some areas of nephrology and generate hypothesis to be tested in future studies.
| N | Year | Authors                                                                 | Title                                                                 | Keywords                                                                 |
|---|------|------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------|
| 1 | 2018  | Maciejczyk, Mateusz; Szulimowska, Julita; Skutnik, Anna; Taranta-Janusz, Katarzyna; Wasilewska, Anna; Wiśniewska, Natalia; Zalewska, Anna | Salivary Biomarkers of Oxidative Stress in Children with Chronic Kidney Disease | chronic kidney disease; salivary biomarkers; oxidative stress; oxidative damage |
| 2 | 2018  | Marzocco, Stefania; Fazeli, Gholamreza; Di Micco, Lucia; Autore, Giuseppina; Adesso, Simona; Dal Piaz, Fabrizio; Heidland, August; Di Iorio, Biagio | Supplementation of Short-Chain Fatty Acid, Sodium Propionate, in Patients on Maintenance Hemodialysis: Beneficial Effects on Inflammatory Parameters and Gut-Derived Uremic Toxins, A Pilot Study (PLAN Study) | propionic acid; chronic kidney disease; hemodialysis; gut microbiome; systemic micro-inflammation oxidative stress; indoxyl sulfate; p-cresyl sulfate |
| 3 | 2018  | Adesso, Simona; Paterniti, Irene; Cuzzocrea, Salvatore; Fujioka, Masaki; Autore, Giuseppina; Magnus, Tim; Pinto, Aldo; Marzocco, Stefania | AST-120 Reduces Neuroinflammation Induced by Indoxyl Sulfate in Glial Cells | indoxyl sulfate; chronic kidney disease; neuroinflammation; glial cells; AST-120 |
| 4 | 2018  | Chaves, Maria; Mendes, Matheus; Schwermann, Maximilian; Queiroz, Raquel; Coelho, Regina; Salmito, Francisco; Meneses, Gdayllon; Martins, Alice; Moreira, Ana; Libório, Alexandre | Angiopoietin-2: A Potential Mediator of the Glycocalyx Injury in Adult Nephrotic Patients | Angiopoietin-2; mediation analysis; nephrotic syndrome |
| 5 | 2018  | Yang, Chen-Ta; Kor, Chew-Teng; Hsieh, Yao-Peng | Long-Term Effects of Spironolactone on Kidney Function and Hyperkalemia-Associated Hospitalization in Patients with Chronic Kidney Disease | chronic kidney disease (CKD); end-stage renal disease (ESRD); major adverse cardiovascular events (MACE); mortality; spironolactone |
| 6 | 2018  | Jhee, Jong; Hwang, Seun; Song, Joon; Lee, Seoung | Upper Normal Serum Creatinine Concentrations as a Predictor for Chronic Kidney Disease: Analysis of 14 Years’ Korean Genome and Epidemiology Study (KoGES) | serum creatinine; estimated glomerular filtration rate; chronic kidney disease; proteinuria |
| 7 | 2018  | Lee, Wen-Chin; Lee, Yueh-Ting; Li, Lung-Chih; Ng, Hwee-Yeong; Kuo, Wei-Hung; Lin, Pei-Ting; Liao, Ying-Chun; Chiou, Terry; Lee, Chien-Ie | The Number of Comorbidities Predicts Renal Outcomes in Patients with Stage 3–5 Chronic Kidney Disease | chronic kidney disease; multimorbidity; renal outcomes |
| N  | Year | Authors                                                                 | Title                                                                 | Keywords                                                                 |
|----|------|-------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------|
| 8  | 2018 | Provenzano, Michele; Minutolo, Roberto; Chiodini, Paolo; Bellizzi, Vincenzo; Nappi, Felice; Russo, Domenico; Borrelli, Silvio; Garofalo, Carlo; Iodice, Carmela; De Stefano, Toni; Conte, Giuseppe; Heerspink, Hiddo; De Nicola, Luca | Competing-Risk Analysis of Death and End Stage Kidney Disease by Hyperkalaemia Status in Non-Dialysis Chronic Kidney Disease Patients Receiving Stable Nephrology Care | CKD; ESKD; death; anti-RAS; hyperkalaemia; competing risk                  |
| 9  | 2018 | Hoi, Shotaro; Takata, Tomoaki; Sugihara, Takaaki; Ida, Ayami; Ogawa, Masaya; Mae, Yukari; Fukuda, Satoko; Munemura, Chishio; Isomoto, Hajime | Predictive Value of Cortical Thickness Measured by Ultrasonography for Renal Impairment: A Longitudinal Study in Chronic Kidney Disease | ultrasonography; kidney size; cortex; CKD risk factors; kidney function |
| 10 | 2018 | Hsu, Po-Ke; Kor, Chew-Teng; Hsieh, Yao-Peng | Effect of New-Onset Diabetes Mellitus on Renal Outcomes and Mortality in Patients with Chronic Kidney Disease | chronic kidney disease (CKD); end-stage renal disease (ESRD); incident diabetes; mortality; new-onset diabetes mellitus (DM) |
| 11 | 2019 | Lee, Keum; Park, Euijin; Choi, Hyun; Kang, Hee; Ha, Il-Soo; Cheong, Hae; Park, Young; Cho, Heeyeon; Han, Kyoung; Kim, Seong; Cho, Min; Lee, Joo; Shin, Jae | Anemia and Iron Deficiency in Children with Chronic Kidney Disease (CKD): Data from the Know-Ped CKD Study | anemia; iron deficiency; chronic kidney disease |
| 12 | 2019 | Tesfaye, Wubshet; Peterson, Gregory; Castelino, Ronald; McKercher, Charlotte; Jose, Matthew; Zaidi, Syed; Wimmer, Barbara | Medication-Related Factors and Hospital Readmission in Older Adults with Chronic Kidney Disease | chronic kidney disease; medication appropriateness index; medication regimen complexity index; the elderly |
| 13 | 2019 | Hsiao, Ching-Chung; Tu, Hui-Tzu; Lin, Chi-Hung; Chen, Kuan-Hsing; Yeh, Yung-Hsin; See, Lai-Chu | Temporal Trends of Severe Hypoglycemia and Subsequent Mortality in Patients with Advanced Diabetic Kidney Diseases Transitioning to Dialysis | advanced diabetic kidney disease; severe hypoglycemia; dialysis |
| 14 | 2019 | Watson, Drew; Yang, Joshua; Sarwal, Reuben; Sigdel, Tara; Liberto, Julianne; Damm, Izabella; Louie, Victoria; Sigdel, Shristi; Livingstone, Devon; Soh, Katherine; Chakraborty, Arjun; Liang, Michael; Lin, Pei-Chen; Sarwal, Minnie | A Novel Multi-Biomarker Assay for Non-Invasive Quantitative Monitoring of Kidney Injury | KIT Assay; chronic kidney disease; biomarker; non-invasive; urine; eGFR; cfDNA |
| N | Year | Authors                                                                 | Title                                                                 | Keywords                                                                                       |
|---|------|-------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| 15 | 2019 [25] | Kim, Chan; Oh, Hyung; Kim, Yon; Kim, Yong-Lim; Chang, Jae; Ryu, Dong-Ryeol | The Effect of Aspirin on Preventing Vascular Access Dysfunction in Incident Hemodialysis Patients: A Prospective Cohort Study in Korean Clinical Research Centers for End-Stage Renal Disease (CRC for ESRD) | aspirin; vascular access failure; incident hemodialysis                                       |
| 16 | 2019 [26] | Di Micco, Lucia; Di Lullo, Luca; Bellasi, Antonio; Di Iorio, Biagio     | Very Low Protein Diet for Patients with Chronic Kidney Disease: Recent Insights | chronic kidney disease; nutritional therapy; urea; phosphorus; metabolic acidosis; vascular calcification; proteinuria; gut; microbiota; cardiovascular risk; very low protein diet |
| 17 | 2019 [10] | Tsai, Shang-Feng; Wu, Ming-Ju; Wen, Mei-Chin; Chen, Cheng-Hsu          | Serologic and Histologic Predictors of Long-Term Renal Outcome in Biopsy-Confirmed IgA Nephropathy (Haas Classification): An Observational Study | IgA nephropathy; patient outcome; renal outcome                                             |
| 18 | 2019 [27] | Mühlig, Anne; Lee, Jun; Kemper, Markus; Kronbichler, Andreas; Yang, Jae; Lee, Jiwon; Shin, Jae; Oh, Jun | Levamisole in Children with Idiopathic Nephrotic Syndrome: Clinical Efficacy and Pathophysiological Aspects | levamisole; nephrotic syndrome; podocyte; steroid-dependent nephrotic syndrome               |
| 19 | 2019 [16] | Bellasi, Antonio; Di Micco, Lucia; Russo, Domenico; De Simone, Emanuele; Di Iorio, Mattia; Vigilante, Raffaella; Di Lullo, Luca; Di Iorio, Biagio | Fractional Excretion of Phosphate (FeP) Is Associated with End-Stage Renal Disease Patients with CKD 3b and 5 | phosphate; phosphate balance; CKD-MBD; outcome; fractional excretion of phosphate; FeP    |
| 20 | 2019 [20] | Mohammed, Chrysan; Xie, Yanmei; Brewster, Pamela; Ghosh, Subhanwita; Dube, Prabhatchandra; Sarsour, Tiana; Kleinhenz, Andrew; Crawford, Erin; Malhotra, Deepak; James, Richard; Kalra, Philip; Haller, Steven; Kennedy, David | Circulating Lactonase Activity but Not Protein Level of PON-1 Predicts Adverse Outcomes in Subjects with Chronic Kidney Disease | paraoxonase; lactonase activity; chronic kidney disease; clinical outcomes                    |
| 21 | 2019 [28] | Russo, Domenico; Tripepi, Rocco; Malberti, Fabio; Di Iorio, Biagio; Scognamiglio, Bernadetta; Di Lullo, Luca; Paduano, Immacolata; Tripepi, Giovanni; Panuccio, Vincenzo | Etelcalcetide in Patients on Hemodialysis with Severe Secondary Hyperparathyroidism. Multicenter Study in “Real Life” | secondary hyperparathyroidism; cinacalcet; etelcalcetide; hypocalcemia; gastrointestinal side effects |
| N  | Year | Authors                                                                 | Title                                                                                                                                             | Keywords                                                                                     |
|----|------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 22 | 2019 | Lee, Yookyung; Kwon, SuYeon; Moon, Jong; Han, Kyungdo; Paik, Nam-Jong; Kim, Won-Seok | The Effect of Health-Related Behaviors on Disease Progression and Mortality in Early Stages of Chronic Kidney Disease: A Korean Nationwide Population-Based Study | chronic kidney disease; disease progression; end stage renal disease; mortality; health-related behaviors; physical activity; smoking; alcohol |
| 23 | 2019 | Alfano, Gaetano; Cappelli, Gianni; Fontana, Francesco; Di Lullo, Luca; Di Iorio, Biagio; Bellasi, Antonio; Guaraldi, Giovanni | Kidney Disease in HIV Infection                                                                                                                  | CKD; chronic kidney disease; nephrotoxicity; HIV; antiretroviral therapy                        |
| 24 | 2019 | Expósito, Carmen; Pera, Guillem; Rodríguez, Lluís; Arteaga, Ingrid; Martínez, Alba; Alumà, Alba; Doladé, Maria; Torán, Pere; Caballeria, Llorenç | Prevalence of Early Chronic Kidney Disease and Main Associated Factors in Spanish Population: Populational Study | chronic kidney disease; prevalence; associated factors; albuminuria; obesity; arterial hypertension; type 2 diabetes |
| 25 | 2019 | Di Iorio, Biagio; Rocchetti, Maria; De Angelis, Maria; Cosola, Carmela; Marzocco, Stefania; Di Micco, Lucia; di Bari, Ighli; Accetturo, Matteo; Vacca, Mirco; Gobetti, Marco; Di Iorio, Mattia; Bellasi, Antonio; Gesualdo, Loreto | Nutritional Therapy Modulates Intestinal Microbiota and Reduces Serum Levels of Total and Free Indoxyl Sulfate and P-Cresyl Sulfate in Chronic Kidney Disease (Medika Study) | CKD; microbiome; indoxyl sulfate; P-cresyl sulfate; very low protein diet; Mediterranean diet |
Conflicts of Interest: The authors declare no conflict of interest.

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